Cerebrospinal Fluid β-Amyloid and Tau Are Not Associated with Risk of Delirium: A Prospective Cohort Study in Older Adults with Hip Fracture

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OBJECTIVES: To examine the association between cerebrospinal fluid (CSF) β-amyloid (Aβ1–42), tau, and hyperphosphorylated tau (Ptau) and risk of delirium in older adults with hip fracture.

DESIGN: Prospective cohort study.

SETTING: University-affiliated general hospital in Alkmaar, the Netherlands.

PARTICIPANTS: Seventy-six participants aged 75 and older admitted for surgical repair of acute hip fracture.

MEASUREMENTS: Presurgical baseline screening and assessment included the Informant Questionnaire on Cognitive Decline—short form (IQCODE-N), Mini-Mental State Examination, standardized Snellen test for visual impairment, Geriatric Depression Scale, Barthel Index (BI), and Lawton Instrumental Activity of Daily Living (IADL) scale. The number of medical comorbidities and medications at home, American Society of Anesthesiologists score, and Acute Physiology and Chronic Health Evaluation II score were determined according to chart review. Delirium was diagnosed using the Confusion Assessment Method. CSF was collected at the onset of spinal anesthesia.

RESULTS: Postoperative delirium occurred in 30 (39.5%) participants. Participants with delirium were older, showed more signs of cognitive decline, were more dependent at home in activity of daily living and IADL functioning, and used more medications before admission. Preoperative CSF Aβ1-42, tau, and Ptau levels were not significantly different in participants who did and did not develop delirium during subsequent hospitalization. In contrast, prefracture cognitive decline (IQCODE-N) was significantly related to delirium (odds ratio = 9.43, 95% confidence interval = 2.45–36.31).

CONCLUSION: Cognitive impairment predisposes to delirium, but in this study, postoperative delirium was not associated with baseline CSF Aβ1-42, tau, and Ptau levels. These findings suggest that CSF markers for plaque and tangle formation are not strongly associated with delirium risk in older adults with hip fracture. **J Am Geriatr Soc 59:1260–1267, 2011.**

Key words: delirium; cerebrospinal fluid; Aβ; tau; hip fracture

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Paper with preliminary results was accepted for oral presentation at the 4th Scientific congress on delirium of the European Delirium Association, Leeds, England, October 8–9, 2009. Paper with preliminary results was accepted for oral presentation at the International Psychogeriatric Association meeting, Santiago de Compostela, Spain, September 26–29, 2010.

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DOI: 10.1111/j.1532-5415.2011.03482.x

Delirium is a serious and common acute neuropsychiatric syndrome in older hospitalized adults and is independently associated with greater long-term risk of death, institutionalization, and dementia.[1] Delirium develops in up to half of older adults after surgery for hip fracture.[2] People with hip fracture constitute a frail population, and those with concomitant cognitive deficits are at particularly high risk of delirium.[3,4] The susceptibility to delirium of individuals with cognitive impairment underlines the strong clinical interrelationship between delirium and dementia, and shared pathogenetic mechanisms for delirium and dementia have been proposed.[5]

0002-8614/11/$15.00

Dementia syndromes are commonly associated with pathological features of Alzheimer's disease (AD) (senile plaques composed of β-amyloid (Aβ1–42) and neurofibrillary tangles consisting of hyperphosphorylated tau (Ptau)).[6] The presence of these pathological features is not limited to individuals with dementia.[7] Up to 40% of individuals aged 80 and older without dementia meet criteria for the neuropathological diagnosis of AD. The presence of these neuropathological lesions in older individuals without dementia is associated with impaired performance in multiple cognitive domains and may represent a preclinical stage of dementia.[8,9]

Neuropathological processes in the brain are thought to be reflected in cerebrospinal fluid (CSF), and biomarkers in CSF have been developed that mirror the presence of Aβ1-42 and tau in the brain.[10] Because the neuropathology of AD can start years before the clinical onset of the disease,[11] it is possible that CSF biomarkers reflect neuronal damage even before any cognitive signs appear.[12]

Although several validated risk models for delirium have been developed, no studies have examined whether CSF Aβ1-42, tau, and Ptau are associated with delirium. The present study examined whether baseline levels of CSF Aβ1-42, tau, and Ptau, as correlates of neuropathological processes that underlie cognitive impairment, are associated with greater risk of delirium. It was hypothesized that lower levels of CSFAβ1-42 and higher levels of tau and Ptau would be associated with a higher incidence of delirium.

METHODS

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki and the guidelines on Good Clinical Practice. Approval of the regional research ethics committee was obtained. All participants gave fully informed written consent.

Study Design and Objectives

Participants were persons in an ongoing clinical trial that compares the effectiveness of taurine with that of placebo in reducing morbidity and 1-year mortality in older adults with hip fracture. (These results will be described elsewhere.) Evaluating the relationship between CSF biomarkers indicative of AD pathology (Aβ1-42, tau, and Ptau) and delirium in older adults with hip fracture was a prespecified secondary aim of this trial. For this purpose, CSF samples were collected at the onset of spinal anesthesia for surgical repair of hip fracture. Other potential risk factors for delirium were also assessed preoperatively. Presence of delirium was assessed daily from time of admission until the fifth postoperative day. Preoperative CSF biomarker Aβ1-42, tau, and Ptau levels and baseline risk factors were compared in participants who did and did not develop delirium during subsequent hospitalization. Because all participants were at high risk of delirium (aged $\geq$75 and acute hospital admission), they received routine care with prophylactic treatment of 0.5 mg haloperidol three times daily from time of admission until postoperative Day 3 unless contraindications regarding its use were present.[13]

Participants

The study was conducted in a series of consecutively admitted older adults with hip fracture to a 706-bed teaching hospital in Alkmaar, the Netherlands. Eligibility was checked for all individuals aged 75 and older admitted for primary surgical repair of hip fracture. Individuals were not eligible if they had no acute trauma, received total hip prosthesis for surgical repair of their hip fracture, had a pathological fracture, were not capable (e.g., dementia in the medical case notes, aphasia, coma) or not willing to provide informed consent, or had contraindications regarding the administration of taurine (renal failure (creatinine clearance $<$30 mL/min)). Written informed consent was obtained after eligibility was checked and the trial had been explained. From March 2008 to March 2009, 122 individuals with hip fracture fulfilled criteria for participation and provided consent (Figure 1).

Measurement and Procedures

Geriatricians, research psychologists, and research nurses trained in delirium assessment and not involved in the clinical care of participants performed all assessments. The members of the research staff performing (preoperative) baseline assessments were the same as those screening for delirium on subsequent days. The research staff was trained to follow standard protocol, and data were collected on standardized precoded forms and checked for errors of validity.

Baseline Assessment

Baseline assessment was completed within 12 hours after admission and before surgery and comprised delirium assessment, participant and proxy interviews and questionnaires, and inspection of the medical record to assess

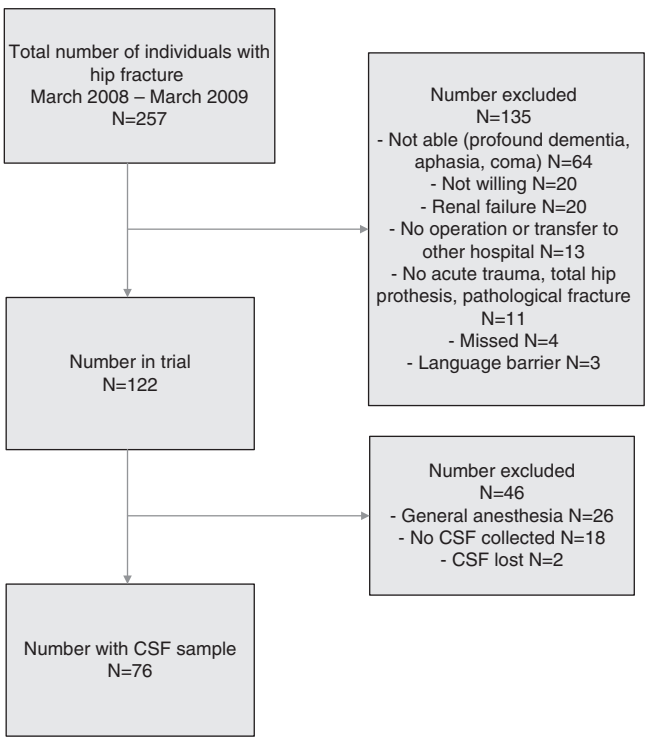

Figure 1. Flow chart.
CSF = cerebrospinal fluid.

relevant risk factors for delirium. Preoperative cognitive functioning was assessed using the Mini-Mental State Examination (MMSE) on a scale of 0 (poor) to 30 (good), with scores lower than 24 indicating cognitive impairment.[14] Prefracture cognitive decline was estimated using the short 16-item version of the Informant Questionnaire on Cognitive Decline (IQCODE-N), which a close relative or caregiver scores and which measures preexistent cognitive decline over the past 10 years on a scale of 16 (improvement) to 80 (decline).[15] A score higher than 57 (mean score of 3.6) indicates cognitive decline.[16] Visual acuity and impairment was assessed using the standardized Snellen test for visual impairment.[17] Visual impairment was defined as binocular near vision, after correction, worse than 20/70. The medical record was reviewed to determine preoperative Acute Physiology and Chronic Health Evaluation (APACHE) II score. The APACHE II score measures severity of acute illness on a scale of 0 (no acute health problems) to 70 (severe acute health problems).[18] The Geriatric Depression Scale (GDS) was administered as a 15-item self-rating scale for depression, with higher scores indicating greater depression.[19] The Barthel Index (BI) was used to determine prefracture functioning in activities of daily living (ADLs) and is scored by a close relative or caregiver on a scale from 0 (dependence) to 20 (independence).[20] Prefracture instrumental activities of daily living (IADLs) were assessed using the Lawton IADL scale (range 8 (no disability) to 31 (severe disability)).[21] Biomedical factors included the number and type of medical comorbidities and medications before admission to the hospital and the American Society of Anesthesiologists (ASA) physical status classification system (range 1 (normal health) to 5 (moribund)).[22] Demographic factors were age, sex, home situation, and educational level. For the IQCODE-N, BI, and Lawton IADL, proxies were asked to describe the participant's condition a week before the fracture to determine function unbiased by the event of hip fracture itself or any acute or subacute event leading to the hip fracture.

Cerebrospinal Fluid

The anesthesiologist collected CSF samples when participants underwent spinal anesthesia for surgical repair of hip fracture. Lumbar punctures were performed using a 25-G needle. CSF samples were obtained using lumbar puncture in the L3–L4 or L4–L5 intervertebral space; 13 mL of CSF was collected in polypropylene tubes and brought to the laboratory within 2 hours. The CSF was centrifuged at 1,800 g for 10 minutes at 4°C and aliquoted into polypropylene tubes that were immediately stored at −80°C until analysis. The CSF samples were sent on dry ice to the laboratory of Clinical Chemistry of the Free University Medical Center, Amsterdam, the Netherlands, with express delivery. Upon arrival, the status of the samples was checked, and they were stored at −80°C until further analysis. Within a few weeks, CSF Aβ1-42, tau, and Ptau were measured using commercially available sandwich enzyme-linked immunosorbent assay (Innogenetics, Ghent, Belgium), as described previously.[23] All CSF analyses were performed at the same time. Because the manufacturer does not supply control specimens, the performance of the assays was monitored with pools of surplus CSF specimens. Performance has been examined for the last 6 years, and stable assay conditions have been established.[24] In the study period, multiple specimens with various concentrations, which were included in seven to 18 runs, were used for this purpose. The mean interassay coefficient of variation ± standard deviation (SD) was 11.3 ± 4.9% for Aβ1-42, 9.3 ± 1.5% for tau, and 9.4 ± 2.5% for Ptau.[24]

Outcome

The main outcome was delirium. Diagnosis of delirium was defined according to the CAM criteria, which consist of acute onset and fluctuating course of cognitive function, inattention, and disorganized thinking or altered level of consciousness.[25] Presence of delirium was assessed within 12 hours after admission and before surgery and continued daily until postoperative Day 5. The CAM rating was based on brief formal cognitive assessment using the MMSE, participant interview, interviews with hospital staff, and scrutiny of the medical and nursing records. CAM ratings were continued until delirium symptoms remitted for 3 consecutive days or until discharge.

Statistical Analysis

Statistical calculations were performed using SPSS for Windows, version 14 (SPSS, Inc., Chicago, IL). Descriptive statistics of the groups with and without delirium are provided in Table 1. Quantitative variables are presented as means ± SDs or medians and (interquartile ranges (IQRs)). Categorical variables were analyzed using chi-square or Fisher exact tests. Continuous variables were tested using Mann-Whitney *U*-tests or *t*-tests depending on the sample size and distribution and skewness of the data. The assumption of a normal distribution of data was tested using the Kolmogrov-Smirnov test. Because the distribution of data of CSF biomarkers was skewed, nonparametric Mann-Whitney *U*-tests were conducted for pairwise comparisons of these variables. Spearman correlation coefficients were used for correlation analyses. The ratios of Aβ1-42 to Ptau and tau to Aβ1-42 were calculated because the predictive value of CSF biomarkers may increase when a combination of Aβ1-42, tau, and Ptau is used.[24,26] Statistical significance was set at $P<.05$. To determine which variables were associated with delirium, standard and stepwise multivariate logistic regression was performed. The intention of the multivariate modelling was not to develop a prediction model for delirium but to test dependencies between the outcome and baseline characteristics. Therefore, this model was not validated, and no correction for overfitting was performed. Variables that were associated with the study outcome in univariate analysis ($P<.10$) were entered as candidate variables in the multivariate models.

RESULTS

One hundred twenty-two of 257 consecutive individuals with hip fracture were included in this study (Figure 1). Twenty-six participants received general anesthesia, and in 18 cases there were logistical limitations that prevented CSF collection (e.g., anesthesiologist did not collect CSF, polypropylene tubes were not available, emergency situation). In two instances, the CSF sample was lost. Individuals without CSF samples were older ($P=.01$) and

Table 1. Baseline Characteristics of Patients with and without Postoperative Delirium

Characteristic	Delirium n = 30 (39.5%)	No Delirium n = 46 (60.5%)	*P*-Value
Age, mean ± standard deviation	84.7 ± 5.1	82.4 ± 4.6	.04
Female, n/N (%)	20/30 (67)	31/46 (67)	.95
Living independently, n/N (%)	24/30 (80)	39/46 (85)	.59
Low educational level, n/N (%)	11/29 (40)	15/44 (34)	.74
Visual impairment,* n/N (%)	2/24 (8)	2/46 (4)	.65
Acute Physiological and Chronic Health Evaluation II† score, median (IQR)	14 (12–14)	13.0 (11–13.8)	.10
American Society of Anesthesiologists‡ group, n/N (%)			.05
I	4/30 (13)	18/46 (39)	
II	18/30 (60)	19/46 (41)	
III	8/30 (27)	9/46 (20)	
Number of comorbid diseases, median (IQR)	2.0 (1.0–3.3)	2.0 (1.0–2.0)	.14
Number of medications at home, median (IQR)	4.5 (3.0–7.3)	3.0 (1.0–6.0)	.03
Informant Questionnaire on Cognitive Decline in the Elderly, Short Form score§			
Median (IQR)	3.6 (3.3–4.2)	3.6 (3.0–3.5)	<.001
>3.6, n/N (%)	18/28 (64)	7/45 (16)	<.001
Mini-Mental State Examination score‖			
Median (IQR)	24 (21.0–25.7)	25.7 (23.5–27.0)	.008
<24, n/N (%)	14/29 (48)	11/45 (24)	.02
Geriatric Depression Scale score, median (IQR)#	2.0 (1.0–4.0)	2.0 (1.0–3.0)	.33
Barthel Index score, median (IQR)**	17.0 (14–19.8)	19.0 (17.0–20.0)	.01
Lawton Instrumental activity of daily living score, median (IQR)††	16.0 (12.0–19.0)	11.0 (8.0–16.0)	.004
Cerebrospinal fluid, pg/mL, median (IQR)			
β-amyloid1–42	631.0 (500.3–985.3)	755.0 (566.5–1,030.8)	.21
Tau	306.0 (231.0–389.0)	324.5 (245.3–511.5)	.75
Hyperphosphorylated tau	71.5 (51.0–80.5)	70.0 (58.5–96.0)	.55

* Measured using the standardized Snellen test for visual impairment and defined as binocular near vision worse than 20/70 after correction.
† Range 0 (no acute health problems) to 70 (severe acute health problems).
‡ Range 1 (normal health) to 5 (moribund).
§ Range 16 (cognitive improvement) to 80 (severe cognitive decline), a score higher than 57 indicates cognitive decline.
‖ Range 0 (severe cognitive impairment) to 30 (no cognitive impairment), score <24 indicates cognitive impairment.
Range 0 (depression not likely) to 15 (depression very likely).
** Range 0 (severe disability) to 20 (no disability).
†† Range 8 (no disability) to 31 (severe disability).
IQR = interquartile range.

had fewer medical comorbidities ($P = .08$). The incidence of postoperative delirium did not differ between individuals with and without CSF samples available for analysis.

Of the 76 participants with CSF samples available, 30 (39.5%) developed delirium according to CAM criteria. None of the participants had preoperative delirium, although 16 scored 1 or 2 points on the CAM during preoperative assessment. Of these 16 participants, nine (56%) developed postoperative delirium. Characteristics of participants with and without delirium are shown in Table 1. Participants with delirium were significantly older, showed more signs of cognitive impairment at baseline and before admission, were more dependent at home in ADL and IADL functioning, and used more medications before admission. Illness severity as measured according to the ASA classification system was greater in participants with delirium, albeit not significant. Other baseline risk factors were not significantly different for those who did and did not develop delirium during hospitalization.

CSF Aβ1-42, tau, and Ptau levels did not differ significantly between participants who did and did not develop delirium during hospitalization (Table 1). Participants with delirium, compared with controls, had a lower median level of Aβ1-42 (631 pg/mL, IQR 500–985 pg/mL, range 211–1,248 pg/mL vs 755 pg/mL, IQR 567–1,031 pg/mL, range 408–1,539 pg/mL; $P = .21$) and tau (306 pg/mL, IQR 231–389 pg/mL, range 134–1,075 vs 325 pg/mL, IQR 245–512 pg/mL, range 101–745 pg/mL; $P = .75$) but a higher level of Ptau (72 pg/mL, IQR 51–81 pg/mL, range 39–176 pg/mL vs 70 pg/mL, IQR 59–96 pg/mL, range 23–171 pg/mL; $P = .55$). Figure 2 shows the distribution of values of CSF biomarkers in participants with and without delirium and illustrates the overlap in individual CSF biomarker levels between the two groups. Similar analyses with the ratios of Aβ1-42 to Ptau and tau to Aβ1-42 led to the same conclusions (data not shown).

Whether CSF biomarkers levels differed between participants with and without preoperative delirium symptoms was also examined. Again, none of the CSF biomarkers nor the ratio of Aβ1-42 to Ptau or tau to Aβ1-42 differed significantly between the two groups (data not shown).

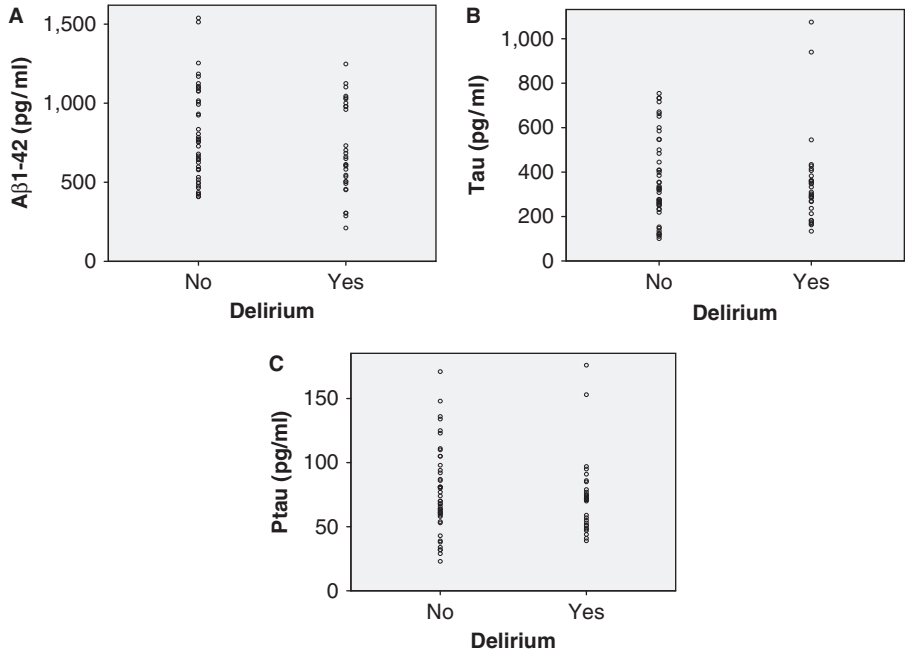

Figure 2. Distribution of preoperative cerebrospinal fluid (A) β-amyloid1-42 (Aβ1-42), (B) tau, and (C) hyperphosphorylated tau (Ptau) levels for participants with and without delirium during subsequent hospitalization.

To examine whether CSF Aβ1-42, tau, and Ptau levels differed between treatment conditions, CSF biomarker levels of the intervention and placebo groups were compared. No differences were found in CSF Aβ1-42, tau, or Ptau levels between the treatment and placebo group, nor was the incidence of delirium different between these two groups.

Factors related to delirium at $P<.10$ in univariate analysis (age, MMSE, IQCODE-N, BI, Lawton IADL, number of medications, ASA) were entered in a logistic regression model (Table 2). Age, prefracture cognitive decline (IQCODE-N), and chronic prefracture illness severity (ASA) were significant at $P<.05$. Using stepwise multivariate logistic regression, prefracture cognitive decline (IQCODE-N) remained the only factor related to delirium (Nagelkerke coefficient of determination (R^2) = 0.28, odds ratio (OR) = 9.43, 95% confidence interval (CI) = 2.45–36.31).

Table 2. Logistic Regression Model of Variables Significantly ($P<.10$) Related to Postoperative Delirium in Univariate Analysis

Factor	*P*-Value	Odds Ratio (95% Confidence Interval)
Age	.03	1.21 (1.02–1.45)
Mini Mental State Examination	.96	1.01 (0.77–1.32)
Informant Questionnaire on Cognitive Decline in the Elderly, Short Form†	.009	18.59 (2.06–167.96)
Barthel Index‡	.23	0.77 (0.50–1.18)
Lawton instrumental activities of daily living§	.07	0.81 (0.64–1.02)
Number of medications at home	.34	1.18 (0.89–1.40)
American Society of Anesthesiologists classification‖	.09	
1	.03	10.94 (1.24–96.46)
2	.20	6.99 (0.37–132.85)

Nagelkerke coefficient of determination = 0.51.
Range 0 (severe cognitive impairment) to 30 (no cognitive impairment).
† Range 16 (cognitive improvement) to 80 (severe cognitive decline).
‡ Range 0 (severe disability) to 20 (no disability).
§ Lawton IADL is Lawton scale, range 8 (no disability) to 31 (severe disability).
‖ Range 1 (normal health patient) to 5 (moribund patient).

The relationship between cognitive functioning and levels of CSF Aβ1-42, tau, and Ptau were explored in additional analyses. Data on cognitive status were lacking for five participants; in three instances, the IQCODE-N was missing, and in two cases, the MMSE was incomplete. Twenty-five of 73 (34%) participants had an IQCODE-N above the cut-off score of 3.6, indicating prefracture cognitive decline. The same percentage of participants (25/74, 34%) scored below the cutoff of 24 on the MMSE, denoting cognitive impairment at baseline. Thirteen of 71 (18%) participants screened positive for cognitive impairment on the IQCODE-N and MMSE, and a moderately strong correlation was found between both scales (Spearman $r^2 = 0.46$, $P<.001$), although no correlation was found between the IQCODE-N and levels of CSF Aβ1-42 (Spearman $r^2 = -0.06$, $P=.61$), tau (Spearman's r^2 0.07, $P=.56$), or Ptau (Spearman $r^2 = 0.04$, $P=.77$). In addition, no association was found between the MMSE and CSF Aβ1-42 (Spearman $r^2 = 0.01$, $P=.91$), tau (Spearman $r^2 = -0.10$, $P=.42$), or Ptau (Spearman $r^2 = -0.04$, $P=.75$). Performing similar analyses with the ratios of Aβ1-42 to Ptau and tau to Aβ1-42 or stratifying the IQCODE-N and MMSE according to the abovementioned cutoff scores did not reveal different outcomes (data not shown).

DISCUSSION

This study found no significant association between preoperative levels of CSF Aβ1-42, tau, or Ptau and subsequent

delirium in older adults hospitalized for surgical repair of hip fracture. These findings suggest that CSF biomarkers that reflect the neuropathological features of AD are not strongly associated with delirium risk in this older population with hip fracture.

Although no relationship was found between delirium risk and CSF biomarkers, prefracture cognitive decline assessed using the IQCODE-N was independently associated with delirium. The strength and significance of this latter association replicates earlier findings indicating that preexisting cognitive impairment is one of the dominant risk factors for delirium in elderly populations.[4] With the informant-based IQCODE-N, one-third of individuals with hip fracture in the current study showed signs of cognitive decline, and two-thirds of these cognitively compromised individuals developed delirium during hospitalization. The IQCODE-N, and not the MMSE, proved to be the strongest risk factor related to delirium. A possible explanation for this finding is that factors associated with hospitalization (e.g., acute illness and prescription of psychoactive medication) can depress performance on the MMSE in a way not characteristic of preexisting cognitive impairment.[27]

The results of this study may be somewhat unexpected, because many studies have shown that CSF biomarkers are associated with dementia and mild cognitive impairment (MCI).[28,29] Cognitive impairment is an important risk factor for delirium, and the group with delirium included more participants with impaired cognitive performance. Therefore, CSF biomarkers levels were also expected to be associated with risk of delirium. Several things may explain the absence of distinct preoperative CSF Aβ1-42, tau, and Ptau differences between participants who did and did not develop postoperative delirium.

The exclusion of individuals with dementia in the medical case notes may have led to the selection of participants with relatively normal cognition and CSF biomarker levels, although 34% of participants in this study showed signs of cognitive decline as measured using the IQCODE-N and MMSE. This is a substantial proportion that is comparable with the prevalence of cognitive impairment in other studies with individuals with hip fracture.[30] Moreover, as noted earlier, the presence of AD pathology is not limited to individuals with dementia only. Individuals with MCI also show aberrant CSF biomarker levels comparable with that of individuals with AD.[29] Post mortem studies have shown that the neuropathological features of AD are also present in up to 40% of older (80–85) individuals without dementia. Furthermore, the presence of these plaques and tangles in older individuals without MCI or dementia is associated with subtle cognitive deficits.[8,9] Thus, although individuals with profound dementia were excluded, a high prevalence of AD neuropathology was most likely present in the group with delirium, as well as in the control group, who were on average aged 80 and older and had a substantial rate of cognitive impairment.

Studies that show that CSF Aβ1-42, tau, and Ptau levels can differentiate dementia and MCI from normal cognition with good accuracy[28,29] are based on participant samples that are 10 to 20 years younger than the age of the current study population. Differences in CSF biomarker levels between people with dementia and controls decrease with advancing age. This attenuation is attributable to older controls showing more AD pathology.[31,32] These findings are consistent with post mortem studies in the oldest old that also show a convergence of the burden of AD pathology between people with dementia and controls.[7] This attenuation suggests that, in the oldest old, additional factors determine the clinical expression of dementia.[7] Thus, although the finding that cognitive impairment is an important predisposing risk factor for delirium was replicated, other processes than plaque and tangle formation likely confer risk for delirium in this older study population. It is possible that coexisting pathological changes frequently seen in older individuals[33] (e.g., vascular changes) may lower the burden of AD pathology required to produce cognitive impairment[7] and thus may confound any association between delirium and Alzheimer's-type pathological features, although a study that compared the occurrence of delirium between different dementia diagnoses found that delirium was more common in late-onset AD and vascular dementia than in early AD and frontotemporal dementia, an effect that differences in age could not explain.[34] Moreover, other studies also suggest that vascular pathology and preexisting white matter damage are linked with delirium risk.[35,36] Thus, other pathological changes known to be causes of dementia may be as important or even more important than plaque and tangle formation in conferring risk for delirium. Additionally, alternative explanations such as an aberrant stress response and overactivation of microglia with resulting neuroinflammation may also be involved in the causation leading to delirium.[37,38]

Several other issues deserve comment. All participants received routine care with prophylactic haloperidol unless there were contraindications to use. Therefore, it was not possible to examine the potential influence of haloperidol prophylaxis on the incidence of delirium, although the treatment regimen used here has been shown to reduce the severity and duration but not the incidence of postoperative delirium.[13] Moreover, a comparison of the rate of delirium in people with hip fracture between the current study and earlier studies conducted in the same medical center suggest no effect of haloperidol prophylaxis on delirium incidence.

Strengths of this study include the collection of CSF, which enabled levels of Aβ1-42, tau, and Ptau to be determined. Because CSF samples were obtained at the onset of spinal anesthesia, ethical and practical challenges associated with CSF collection were avoided. Moreover, CSF Aβ1-42, tau, and Ptau levels were analyzed in a specialized laboratory that has established good interassay variability. The laboratory's standardized protocol for CSF collection, handling, and storage was used, so important sources of variance that may otherwise have reduced the validity of the findings were avoided.[39,40] Another strength is that participants and proxies underwent detailed preoperative assessment, which allowed CSF biomarkers to be compared with participant and informant measures of cognitive impairment. Furthermore, a systematic assessment of delirium using standardized and well-validated instruments was used. Also, participants were assessed within 12 hours after hospital admission and before surgery and were screened daily for symptoms of delirium.

Several limitations of the current study should also be addressed. First, this study was not specifically powered to examine the association between CSF biomarkers and

delirium. Therefore, definitive conclusions on the absence of an association between delirium and CSF Aβ1-42, tau, and Ptau can not be drawn because a type II error can not be excluded, but when evaluating the overlap of CSF biomarker levels between participants with and without delirium and the associated *P*-values (illustrated in Figure 2), the absence of a relationship seems apparent. The modest number of participants included in this study also limits the interpretation of the regression analyses, but the intention of the multivariate analyses was not to develop and validate a prediction model for delirium. Instead, it was desired to test dependencies between the outcome and baseline characteristics and investigate the importance of cognitive impairment, relative to other baseline characteristics, as a predisposing risk factor for delirium. Because there were only 30 cases of delirium, a model with more than three factors (Table 2) might have been inappropriate, so the interpretation of the findings of the multivariate model should be limited to the observation that, despite the absence of an association between delirium and CSF biomarkers, cognitive impairment remains an important risk factor for delirium. Another caveat is that this study represents a combination of the intervention and control arms of a randomized trial. Although this study would ideally have been performed in an observational cohort, the sample size would have been substantially smaller when the analyses were performed only in the placebo condition. Moreover, no differences were found in CSF biomarker levels or incidence of delirium between the intervention and placebo groups.

In conclusion, this is the first study to address the important question whether CSF biomarkers that reflect plaque and tangle formation in the brain are associated with delirium in older adults with hip fracture. Although delirium was more often present in participants with cognitive decline than in those without cognitive impairment, delirium was not clearly associated with CSF Aβ1-42, tau, or Ptau levels, suggesting that factors related to pathological processes other than plaque and tangle formation predispose older adults with hip fracture to delirium, although no definitive conclusions can be drawn on the nature of these causal factors in this older adult population.

ACKNOWLEDGMENTS

Joost Witlox had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

We would like to thank Gisela Dekker, RN (data acquisition, administrative, technical or material support), Ralph Vreeswijk, RN, MSc (data acquisition), Milko van Langen (data acquisition), Tjerk Schoemaker, MSc (data acquisition), Margreet Schoorl, RN (administrative, technical and material support), and Tjeerd van der Ploeg, MSc (data analysis, administrative, technical or material support) for their work on the study.

Conflict of Interest: AMJM was supported by a Medical Research Council Clinician Scientist Fellowship.

Author Contributions: Joost Witlox: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for intellectual content, statistical analysis, administrative, technical and material support. Kees J. Kalisvaart and Jos F. M. de Jonghe: study concept and design, analysis and interpretation of data, critical revision of the manuscript for intellectual content, administrative, technical and material support, study supervision. Niek Verwey: study concept and design, analysis and interpretation of data, critical revision of the manuscript for intellectual content, administrative, technical and material support. Mireille F.M. van Stijn and Han S. Traast: acquisition of data, critical revision of the manuscript for intellectual content, administrative, technical and material support. Alexander P.J. Houdijk: critical revision of the manuscript for intellectual content, administrative, technical and material support. Alasdair M.J. MacLullich: study concept and design, analysis and interpretation of data, critical revision of the manuscript for intellectual content. Willem A. van Gool: study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for intellectual content, study supervision. Piet Eikelenboom: study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for intellectual content, administrative, technical and material support, study supervision.

Sponsor's Role: None.

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