Serum pNF-H, a potential predictive biomarker for postoperative cognitive dysfunction in elderly subjects undergoing hip joint replacement

Huafeng Zhang
Ningbo No 2 Hospital
Jinwei Zheng
Ningbo No 2 Hospital
Ruichun Wang
Ningbo No 2 Hospital
Guorong Wu
Ningbo No 2 Hospital
Junping Chen (yunfeiyangtg@126.com)
Ningbo No 2 Hospital https://orcid.org/0000-0003-1381-9966

Research Article

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Abstract

Background: Postoperative cognitive dysfunction (POCD), which refers to a cognitive impairment subsequent to surgical procedures, is a common complication in the elderly subjects. This study aimed to investigate potential risk factors for POCD in elderly subjects undergoing hip joint replacement.

Methods: Consecutive elderly osteoarthritis patients who were scheduled to undergo hip replacement under epidural anesthesia were enrolled into this single-center, prospective observational study. Serum phosphorylated neurofilament heavy subunit-H (pNF-H) was measured by the enzyme-linked immuno sorbent assay (ELISA) method. A level of >70.5 pg/mL was accepted as pNF-H positivity. Neuropsychological assessment at baseline (one day before the surgery) and postoperative day 7 was conducted. POCD was defined according to the calculated Z scores. Risk factors for POCD were evaluated by univariate and multivariate logistic regression analyses.

Results: In final, 287 patients were enrolled and 55 had suffered POCD within postoperative 7 days with an incidence of 19.2%. The final multiple logistic regression analysis revealed a higher pNF-H positivity was the only independent risk factor for POCD (OR: 2.03, 95%CI: 1.21-3.29, P=0.012)

Conclusions: Our results revealed an increased preoperative serum pNF-H expression was an independent risk factor for POCD development in elderly subjects undergoing hip joint replacement, suggesting the close association between anatomical damage in central nervous system (CNS) and POCD.

Key words: Postoperative cognitive dysfunction; elderly; hip joint replacement; pNF-H; biomarker

Introduction

Postoperative cognitive dysfunction (POCD), a common complication in the elderly subjects, refers to a cognitive impairment subsequent to surgical procedures, especially the decline in executive functions and memory (1). As reported by previous evidence, the incidence of POCD ranges from 8.9% to 46.1% with elusive pathophysiology (2). During those patients aged over 60 years undergoing non-cardiac surgery, the incidence of POCD was reported to be 25.8% at 1 week and 9.9% at 3 months by the International Study of Postoperative Cognitive Dysfunction (ISPOCD) (3). Due to the elusive pathophysiology and complicated neuropsychological testing requirements, the diagnosis of POCD is always delayed. The onset of POCD is an important cause of prolonged hospital stay, poorer social outcomes, morbidity and mortality after major operations (4). Thus, it is of crucial importance to identify noninvasive and reliable biomarkers for POCD prediction and risk stratification.

Phosphorylated neurofilament heavy subunit-H (pNF-H), a major structural protein in central nervous system (CNS) axons, shows an adequate sensitivity for the spinal cord injury (5). Increased pNF-H expressions have been reported to be significantly associated with CNS damage (6). Among animals, low pNF-H expression is reported closely associated with increased cell death (7). PNF-H is also involved in axonal regeneration and it is suggested as a good measure of brain damage, as well as axonal recovery

(8). A recent study has suggested the potential application of pNF-H as a biomarker of neural damage among patients undergoing chemotherapy for breast cancer (9). pNF-H is also an effective predictive biomarker for postoperative delirium among patients who underwent surgery for abdominal cancer (10). However, whether it can serve as a predictor for POCD in elderly patients undergoing hip joint replacement remains unclear. This study aimed to identify potential predictors for POCD in elderly patients with hip joint replacement.

Methods

This study protocol was approved by the Medical Institutional Ethics Committee of Ningbo No. 2 hospital and Zhejiang province. This investigation was a single-center, prospective observational study which was conducted in the Department of anesthesiology from July 2015 to July 2017. Consecutive elderly osteoarthritis patients who were scheduled to undergo hip replacement under epidural anesthesia were enrolled. All the enrolled patients provided written informed consent before the surgery. Inclusion criteria: (1) aged between 65 and 80 years; (2) American Society of Anesthesiologists (ASA) grade II or III; (3) undergoing first-time unilateral total hip joint replacement under epidural anesthesia. The exclusion criteria: (1) with preexisting neurological disease or psychiatric disorder; (2) preoperative Mini-Mental State Examination (MMSE) score <24; (3) with a history of cardiovascular or neurosurgical surgery; (4) with alcohol or drug dependence; (5) inability to read or speak, with vision or hearing impairment; (5) with low compliance; (6) loss to follow-up or with no completed data.

Neuropsychological assessment and POCD definition

Neuropsychological assessment at baseline (one day before the surgery) and postoperative day 7 was conducted following the guidance of previous consensus statement (11). As widely described by previous reports, the test battery included Digit span test, MMSE, Trail making test (part A), Word recognition memory tests, Verbal fluency test and Symbol digit test (12). According to the guidance of International Study of Postoperative Cognitive Dysfunction (ISPOCD1 and ISPOCD2), a Z score for each test was calculated (3, 13). In this study, patients were defined as suffering POCD while at least two Z scores $\geq$ 1.96 (14).

Clinical data collection

The following perioperative clinical data were recorded: (1) demographic data including age, gender, Body Mass Index (BMI), ASA physical status, smoking habits; (2) Preoperative comorbidities including diabetes, hypercholesterolemia, hypertension, peripheral vascular disease, history of myocardial infarct; (3) preoperative medications including angiotensin-converting enzyme (ACE) inhibitors,β-blockers, and statins; (4) other clinical data including preoperative MMSE, duration of surgery and anesthesia, recovery time, estimated blood loss, blood transfusion.

Laboratory tests

Fasting blood samples from all the enrolled patients were obtained at one day before the surgery (baseline). Serum samples were obtained after centrifugation (3000 rpm, 10min, 4°C) and then stored at -80°C for further laboratory tests. The inflammatory biomarkers including C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) were measured by the enzyme-linked immuno sorbent assay (ELISA) method using kits (R&D Systems, Minneapolis, MN, USA). The serum expression of pNF-H was detected using human pNF-H ELISA kit (BioVendor, Modrice, Czech Republic) following the guidance of the manufacturer's protocol. The obtained serum samples were diluted three fold before the pNF-H detection. A level of >70.5 pg/mL was accepted as pNF-H positivity according to previous reports (5). The preoperative blood analyses (including hemoglobin, white blood cell) and blood biochemical examinations (including albumin, creatinine, urea) were also detected by the laboratory in our hospital.

Statistical analysis

GraphPad Prism 5.0 (GraphPad Inc., CA, USA) and SPSS 19.0 (SPSS, Inc., IA, USA) were utilized for the data analysis. Continuous and categorical data were presented as mean and standard error (S.E.M), number (n) and percentage (%), respectively. Mann-Whitney U test, t test, Chi-square test and Fisher exact test were used for data analyses as appropriate. Risk factors for POCD were evaluated by univariate and multivariate logistic regression analyses. All statistical analyses were bilateral probability and a P value of <0.05 was considered statistically different.

Results

Patient characteristics

According to the inclusion criteria, a total of 351 eligible elderly osteoarthritis patients were screened for the study. 64 were excluded due to the exclusion criteria, 5 with preexisting neurological disease, 7 with a history of cardiovascular surgery, 6 with alcohol dependence, 6 inability to read or speak, 15 with low compliance and 25 with no completed data. In final, 287 patients were enrolled and 55 had suffered POCD within postoperative 7 days with an incidence of 19.2%. Table 1 compares the characteristic of patients with POCD or without POCD development. As shown, no significant differences among gender distribution, BMI, ASA phrase status, smoking habits, preoperative medications, recovery time and blood transfusion were observed between them (P>0.05). Patients with POCD showed a significantly higher age comparing with those without POCD (71.3±3.3 vs 70.2±2.9, P=0.014). The incidences of preoperative comorbidities (diabetes and hypertension) were also statistically different between the two groups (P=0.028 and P=0.046, respectively). A lower preoperative MMSE score seemed to be associated with an increased risk of POCD development (P=0.033). In respect to the operation indexes, a longer duration of surgery and anesthesia, higher estimated blood loss were observed in patients with POCD (P<0.05).

Laboratory tests

Table 2 summarizes the results of laboratory tests between two groups. Patients who suffered POCD showed an obviously increased serum expressions of CRP and TNF-α (P<0.05). At the onset of POCD, 10

(10/55, 18.2%) patients demonstrated pNF-H positivity, which was quite higher than those patients without POCD (16/232, 6.9%, P=0.009).

Risk factors for POCD

As shown in Table 3, ten potential risk factors mentioned above were included into the univariate and multivariate logistic regression analyses. As illustrated by the univariate analysis, age, preoperative MMSE, CRP and pNF-H positivity were 4 risk factors for POCD (P<0.05). The final multiple logistic regression analysis revealed a higher pNF-H positivity was the only independent risk factor for POCD (OR: 2.03, 95%CI: 1.21-3.29, P=0.012)

Discussion

POCD is a great attack and challenge for those patients who undergo major surgery, especially for the elderly subjects (15). A review by Dariusz has reported that the incidence of POCD in orthopedic subjects varies from 16% to 45% (16). The incidence of POCD in our study was 19.2% (55/287), which was quite similar to 19.6% reported by Rong et al.(14). As verified repeatedly, increased age is significantly associated with the increased risk of developing POCD (17), which is in accordance with our results of univariate analysis. Preexisting cognitive impairment has been reported to be closely associated with POCD in subjects undergoing hip joint replacement (18). Our univariate analysis also indicated preoperative MMSE score as a risk factor for POCD development. The close correlation between inflammatory marker concentrations, especially CRP, and POCD has been widely revealed (19, 20), which supports the pathogenic role of inflammation in POCD. However, our results from the final multivariate logistic regression analysis didn't support the predictive roles of these three parameters in POCD. In our opinion, the differences in sample size, inclusion and exclusion criteria, patient characteristics, preoperative comorbidities and the time of blood sampling might be possible explanations for the different conclusions.

In this present study, elevated serum pNF-H positivity was significantly associated with an increased risk of POCD in elderly subjects undergoing hip joint replacement. This finding suggested a potential application of serum pNF-H as a predictor for POCD development. As proved by previous studies, pNF-H may serve as an effective and reliable biomarker for CNS damage (6, 9). Our results directly revealed that POCD might be associated with anatomical damage in CNS. Previous studies have revealed the close association between pNF-H expression and the severity of spinal cord injury (5). Serum pNF-H has also been suggested as an effective biomarker for therapeutic efficacy evaluation among patients with spinal cord injury (21). Elevated pNF-H expressions are widely observed in those patients with supraspinal CNS damage caused by various conditions, such as acute intracerebral hemorrhage (22), hypoxic-ischemic encephalopathy (23) and febrile seizures (24).

Increased serum pNF-H concentrations are also observed in patients undergoing chemotherapy for breast cancer, suggesting the application of pNF-H as a potential biomarker of neural damage induced by chemotherapy (9). A close correlation between biomarkers of brain damage and POCD has been reported

in orthopedic patients by previous literature (16), which strongly suggests the critical role of brain damage in POCD development. A recent report has revealed that pNF-H levels in patients undergoing operations for cervical compressive myelopathy are not elevated (25). In respect to our results, serum pNF-H may serve as a good candidate for POCD assessment. It might be beneficial to investigate the involved mechanisms using pNF-H as a surrogate biomarker for POCD development. The use of pNF-H detection as the potential biomarker for POCD can help to elucidate the potential role of anatomical brain damage in the mechanisms of POCD.

Conclusisons

In conclusion, our results revealed an increased preoperative serum pNF-H expression was an independent risk factor for POCD development in elderly subjects undergoing hip joint replacement, suggesting the close association between anatomical damage in CNS and POCD.

Abbreviations

POCD, postoperative cognitive dysfunction; ISPOCD, International Study of Postoperative Cognitive Dysfunction; pNF-H, phosphorylated neurofilament heavy subunit-H; CNS, central nervous system; ASA, American Society of Anesthesiologists; MMSE, Mini-Mental State Examination; BMI, Body Mass Index; ACE, angiotensin-converting enzyme; CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; ELISA, enzyme-linked immuno sorbent assay; CI: Confidence Interval; OR, Odds Ratio.

Declarations

This study was approved by the Medical Institutional Ethics Committee of Zhejiang province. The patients enrolled all presented written informed consent.

Consent to Publish

Yes.

Competing interests

None.

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Authors' contributions

HF Z, JW Z participated in the conception and design, data collection, statistical analysis and wrote the manuscript. RC W, GR W and JP C participated in the conception and design and data collection.

Availability of Data and Materials

Yes.

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Tables

Table 1. Demographic and clinical data of patients with or without POCD

Variables	POCD（n=55）	Non-POCD（n=232）	*P*-value
Age (year)	71.3±3.3	70.2±2.9	0.014
Gender, n (%)			0.393
Male	20(36.4)	99(42.7)	-
Female	35(63.6)	133(57.3)	-
BMI (kg/m^2)	23.1±2.7	22.8±2.3	0.401
ASA physical status, n (%)			0.431
II	30(54.5)	140(60.3)	-
III	25(45.5)	92(39.7)	-
Active smoker, n (%)	11(20.0)	37(15.9)	0.469
Preoperative comorbidities, n (%)			
Diabetes	12(21.8)	25(10.8)	0.028
Hypercholesterolemia	11(20.0)	39(16.8)	0.575
Hypertension	16(29.1)	40(17.2)	0.046
Peripheral vascular disease	4(7.3)	14(6.0)	0.734
History of myocardial infarct	5(9.1)	20(8.6)	0.912
Preoperative MMSE (score)	27.4±1.7	28.0±1.9	0.033
Preoperative medications			
ACE inhibitors	11(20.0)	37(15.9)	0.469
β-blockers	8(14.5)	34(14.7)	0.984
Statins	9(16.4)	30(12.9)	0.504
Duration of surgery (min)	118.3±33.3	107.8±29.1	0.020
Duration of anesthesia (min)	165.5±38.1	153.8±32.5	0.023
Recovery time (min)	40.5±10.7	40.2±11.1	0.857
Estimated blood loss (ml)	691.4±122.7	654.2±105.7	0.024
Blood transfusion, n (%)	13(23.6)	34(14.7)	0.106

ASA, American Society of Anesthesiologists; BMI, Body Mass Index; MMSE, Mini-Mental State Examination; ACE, angiotensin-converting enzyme; POCD, Postoperative Cognitive Dysfunction. *P*-values were calculated by Chi-square test, Fisher exact test, Mann–Whitney U-test or t test. * *P* value<0.05.

Table 2. The laboratory tests of patients with or without POCD

Variables	POCD（n=55）	Non-POCD（n=232）	P-value
Hemoglobin (g/dL)	11.4±1.7	11.8±1.8	0.136
White blood cell (x10^9/L)	7.3±2.0	6.9±1.8	0.148
CRP (mg/L)	13.1±4.1	12.0±3.4	0.039
IL-6 (pg/mL)	18.1±7.8	17.5±6.7	0.564
TNF-α(nmol/L)	8.0±2.2	7.4±1.7	0.028
Albumin (g/mL)	40.1±4.2	39.8±3.5	0.583
Creatinine(mmol/L)	84.1±18.1	82.3±20.1	0.544
Urea(mmol/L)	6.7±2.1	6.3±1.9	0.170
pNF-H positivity, n (%)	10(18.2)	16(6.9)	0.009

POCD, Postoperative Cognitive Dysfunction; CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; pNF-H, phosphorylated neurofilament heavy subunit-H. *P*-values were calculated by Mann–Whitney U-test or t test. * *P* value<0.05.

Table 3. Univariate and multiple logistic regression analyses for POCD

	Univariate		Multivariate	
Variables	OR(95%CI)	*P* value	OR(95%CI)	*P* value
Age	2.12(1.05–4.41)	0.028*	1.47(0.31–2.45)	0.63
Diabetes	1.22(0.58-2.51)	0.54		
Hypertension	1.63(0.76-3.57)	0.22		
Duration of surgery	1.74(0.82-3.66)	0.15		
Duration of anesthesia	1.95(0.87-4.35)	0.11		
Preoperative MMSE	0.41(0.19–0.92)	0.022*	0.66(0.31–1.52)	0.38
Estimated blood loss	1.12(0.83-1.49)	0.16		
CRP	2.67(1.41–3.94)	0.025*	1.41(0.75-2.84)	0.17
TNF-α	1.05(0.73-1.44)	0.85		
pNF-H positivity	2.49(1.69-3.74)	0.009	2.03(1.21-3.29)	0.012

POCD, Postoperative Cognitive Dysfunction; CRP, C-reactive protein; TNF-α, tumor necrosis factor-α; MMSE, Mini-Mental State Examination; CI: Confidence Interval; OR, Odds Ratio. * *P* value<0.05.