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Serum levels of apolipoprotein A-I and E are associated with postoperative delirium

A post hoc analysis

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Abstract

Postoperative delirium is a common complication for elderly patients. Detection of phosphorylated neurofilament heavy subunit in the serum reflects axonal damage with postoperative delirium. Although it has been implicated that serum apolipoprotein levels might be associated with senile cognitive disorder, its role in the development of delirium has not been fully investigated. This study examined the association of apolipoproteins with delirium after surgery.

This was a post hoc analysis of 117 patients who participated in a prospective observational study of delirium in patients undergoing cancer surgery. Patients were clinically assessed for delirium within the first 5 days of surgery. Serum levels of apolipoprotein A-I, B, and E were measured on postoperative day 3.

Forty-one patients (35%) were clinically diagnosed with postoperative delirium. Serum levels of apolipoprotein A-I and B were increased in patients with delirium whereas those of apolipoprotein E were decreased. These changes in apolipoprotein A-I and E levels were associated with the presence of phosphorylated neurofilament heavy subunit in the serum, and were significantly associated with delirium (A-I: adjusted odds ratio [aOR], 6.238; 95% confidence interval [CI], 2.766–20.68; $P < .0001$; E: aOR, 0.253; 95% CI, 0.066–0.810; $P = .0193$). A combination of apolipoprotein A-I and E offers significant discrimination between delirium and nondelirium with high accuracy (area under the curve, 0.8899).

Serum apolipoprotein A-I and E levels were associated with delirium and the presence of phosphorylated neurofilament heavy subunit in serum. Therefore, apolipoproteins might be useful biomarkers of postoperative delirium.

Abbreviations: AD = Alzheimer's disease, Apo = apolipoprotein, AUC = area under the curve, CAM = confusion assessment method, CSF = cerebrospinal fluid, MRI = magnetic resonance imaging, pNF-H = phosphorylated neurofilament heavy subunit, ROC = receiver operating characteristic.

Keywords: apolipoprotein, phosphorylated neurofilament heavy subunit, postoperative delirium.

1. Introduction

Apolipoproteins have important roles in the pathophysiology of cognitive disorders.[1] It is thought that plasma levels of apolipoprotein (Apo), including ApoA-I, ApoB, and ApoE, are potential biomarkers that predict dementia. ApoA-I is directly involved in cholesterol efflux in the brain[2] and was a highly significant predictor of cognitive decline.[1] Elderly individuals with mild cognitive impairment had lower levels of ApoA-I, and a higher ApoB/ApoA1 ratio and levels of ApoE. ApoE levels were negatively correlated with gray matter volume and positively correlated with cerebrospinal fluid (CSF) volume on magnetic resonance imaging (MRI).

In contrast, lower serum levels of ApoB in elderly adults with subjective cognitive decline were associated with increases in

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Trial registration: University Medical Information Network (UMIN) trial ID: UMIN000010329.

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CSF p-tau/Abeta 42 independent of *APOE*ε4 status,[3] which is a major genetic risk factor for Alzheimer disease (AD), increasing the risk of disease and decreasing the age of disease onset.[4] In patients with delirium, the *ApoE4* status was not associated with delirium.[5] Rather, a reduction in absolute CSF apolipoprotein E level was observed during delirium, which correlated with Confusion Assessment Method (CAM) scores.[6]

Although the involvement of Apo in the development of progressive cognitive disorder has been reported, its role in postoperative delirium is poorly understood. We recently reported that serum phosphorylated neurofilament heavy subunit (pNF-H), an axonal cytoskeletal proteins detected in the serum, was associated with the onset of postoperative delirium.[7] To further elucidate the mechanism of delirium, we investigated serum ApoA-I, ApoB, and ApoE levels in patients undergoing cancer surgery with or without delirium during the postoperative period.

2. Methods

2.1. Ethics

This study was conducted at The University of Tokyo Hospital, Saitama Red Cross Hospital, and Tsukuba University Hospital. This study was approved by the institutional review board [10051]. Written informed consent was obtained from each patient before participating in the study. This study was registered in the University Medical Information Network (UMIN trial ID: UMIN000010329).

2.2. Study population

Patients undergoing cancer surgery were enrolled and followed-up in this study between July 23, 2013, and February 28, 2015. The present study used their stored serum samples from enrolled patients.[7] Part of the data including the exclusion criteria, patient demographics, and the positivity of pNF-H were previously published.[7]

2.3. Patient assessment

Patients were assessed for delirium-associated symptoms using the Confusion Assessment Method in the Intensive Care Unit by nurses and the Intensive Care Delirium Screening Checklist by investigators.[7] Blood sampling was performed on day 3 based on the previous reports where delirium onset was clustered around postoperative days 1–3.[8,9] pNF-H (Human Phosphorylated Neurofilament H ELISA; BioVendor, Modrice, Czech Republic), Apo A-I, ApoB, and ApoE (SEKISUI, Tokyo, Japan) concentrations were determined using a modified enzymatic assay and a biochemical automatic analyzer (BM6030 [JEOL, Tokyo, Japan]). The threshold for pNF-H positivity ($70.5\,ng.ml^{-1}$) was determined according to the manufacturer's instructions.

2.4. Statistical analysis

All analyses were performed based on the log-transformed concentration of the potential candidate variables. Patient biomarker levels were compared using the Wilcoxon signed rank test. To identify biomarkers for postoperative delirium diagnosis or detection of CNS-derived pNF-H in the serum, we conducted Receiver Operating Characteristic (ROC) analyses. Subsequently, multiple logistic regression was performed using the variables found to be most relevant ($P < .05$) by univariate analysis. Linear discriminant analysis was performed followed by ROC analysis. Analyses were performed using JMP Pro version 15 (SAS Institute, Cary, NC, USA) or SPSS software version 22 (IBM Corp, Armonk, NY, USA). $P \leq .05$ was considered significant.

3. Results

Age was significantly associated with delirium (Table 1, Supplemental Digital Content, http://links.lww.com/MD/G964). Serum levels of ApoA-I ($P < .0001$) and ApoB ($P < .0001$) were significantly higher in patients with delirium compared with those without delirium, whereas those of ApoE levels ($P < .0001$) were lower in patients with delirium compared with those without delirium on the postoperative day 3 (Fig. 1). The area under the curve of serum ApoA-I, ApoB, and ApoE levels to predict delirium were 0.84 (sensitivity, 0.68; specificity, 0.97), 0.69 (sensitivity, 0.61; specificity, 0.82), and 0.81 (sensitivity, 0.68; specificity, 0.92), respectively. Serum ApoA-I, ApoB, and ApoE levels were significantly associated with the development of delirium (Table 1). However, only serum levels of ApoA-I and ApoE were associated with predicting the presence of pNF-H (Table 2). Therefore, linear discriminant analysis was performed to predict postoperative delirium with a combination of ApoA-I with ApoE as variables (Fig. 2). A combination of ApoA-I and ApoE highly discriminated between delirium and nondelirium (Wilks' lambda = 0.499, $P < .001$) with an error rate of 12.82%. The mean squared canonical correlation was 0.708. The discriminative function equation (composite score) was as follows: 0.804 for ApoA-I and – 0.823 for ApoE. The ROC curve showed 87.2% overall correct classification in discriminating between delirium and nondelirium, with a sensitivity of 65.9%, specificity of 98.7%, and area under the curve of 0.8899.

4. Discussion

Serum levels of ApoA1 and ApoB were increased in patients with delirium compared with those without delirium, whereas those of ApoE were decreased in the postoperative periods (Fig. 1). These results were consistent with a previous report where the absolute CSF apolipoprotein E levels were reduced during delirium.[6] Although it was reported that plasma levels of some apolipoproteins, especially ApoE, were associated with lifespan and cognitive function in elderly individuals,[10] the differences in apolipoproteins between delirium and nondelirium patients were significant ($P < .0001$) even when the analysis was performed with age as a covariate (data not shown in Fig. 1). In addition, all these markers were associated with delirium (Table 1); however, ApoA-I and ApoE, but not ApoB, were associated with the presence of pNF-H, which was detected in the serum of cases with CNS axonal damage (Table 2). It was reported that elderly patients experienced an increased rate of brain atrophy during 5 to 9 months after surgery, a period associated with an enhanced risk for postoperative cognitive dysfunction.[11] Similarly, greater brain atrophy (higher ventricle-to-brain ratio) at 3 months after discharge from the intensive care unit was associated with worse cognitive performances at 12 months.[12] Because ApoE levels were negatively correlated with gray matter volume on the MRI of cases with mild cognitive impairment,[3] our results showing the serum level of ApoE on postoperative day 3 was negatively associated with the levels of pNF-H suggests that ApoE levels might predict brain atrophy and the exacerbation of cognitive performance in the acute postoperative period. In contrast, the results of discriminant analysis suggested that ApoA-I may directly reflect the exacerbation of axonal damage induced after surgery (Fig. 2). Our study suggests 2 potential strategies for delirium. First, a combination of ApoA-I and ApoE can discriminate between delirium and nondelirium patients with high accuracy. Second, treatment that suppresses ApoA-I levels or augments ApoE levels might prevent the onset of postoperative delirium. However, a study limitation was that changes in apolipoproteins were not evaluated. Therefore, it is still unclear whether the serum levels of ApoA-I, ApoB, and ApoE on postoperative day 3 reflect exacerbation or recovery from delirium status. In addition, the ApoE genotype, highly associated with

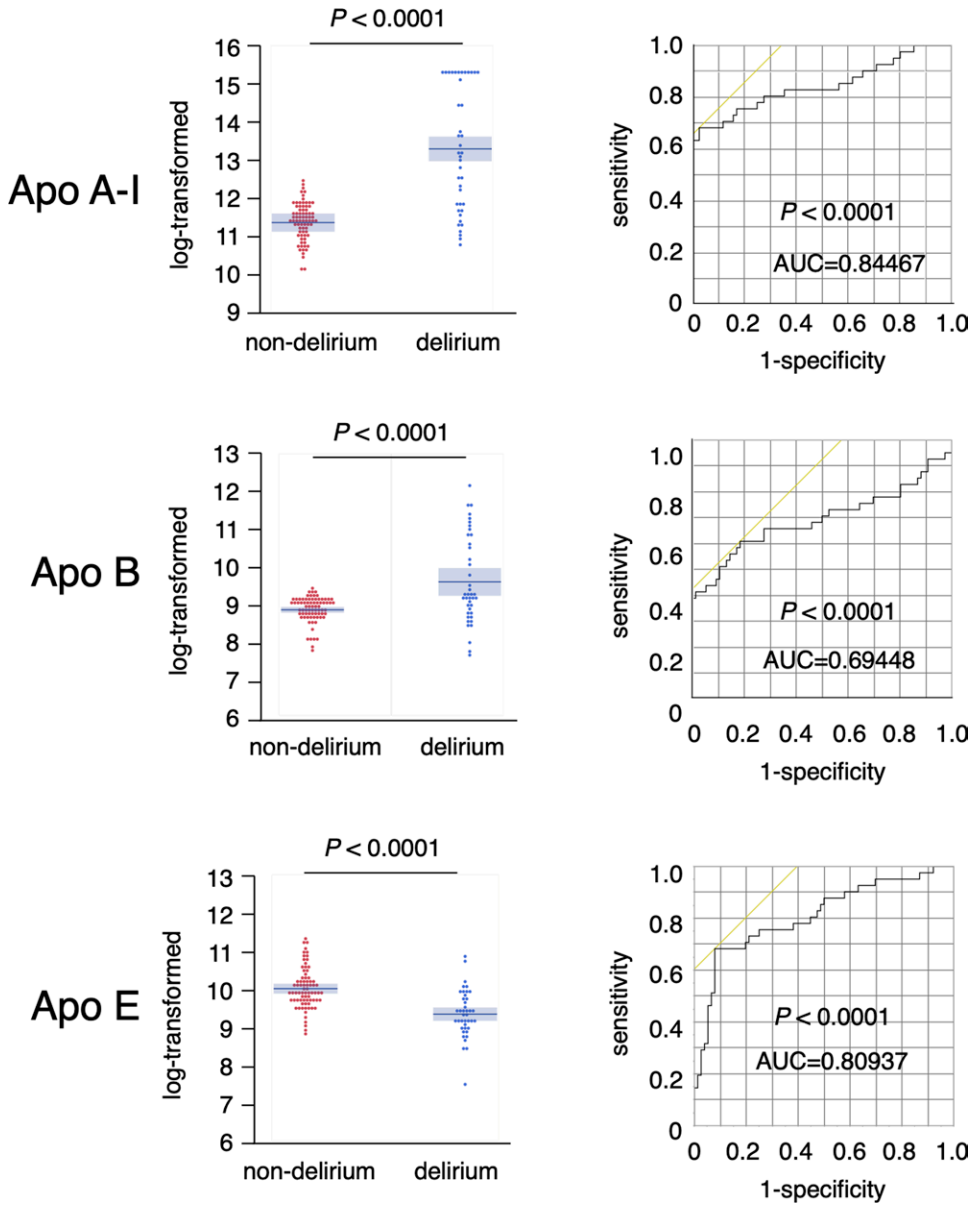

Figure 1. Comparison of serum apolipoprotein levels between delirium and nondelirium patients. (A) The levels of Apo A-I, Apo B, and ApoE were compared between groups by the Wilcoxon signed rank test. (B) ROC analysis of Apo A-I, Apo B, and ApoE to discriminate between delirium and nondelirium patients. Apo = apolipoprotein, AUC = area under the curve.

Table 1

Logistic regression analysis for diagnosing delirium.

	Crude OR	95% CI	*P*	Adjusted OR	95% CI	*P*
log Apo A-I	6.998947	3.385–18.845	<.0001	6.238085	2.758–20.677	<.0001
log Apo B	4.129447	2.160–9.862	<.0001	3.455464	1.151–17.933	.0240
log Apo E	0.09537	0.032–0.238	<.0001	0.25311	0.0661–0.811	.0193

†Apo, apolipoprotein;
‡OR, odds ratio;
§CI, confidential interval

the production of tau and Ab42,[4] was not evaluated. Recently, it was reported that a change in plasma tau from preoperative concentrations to postoperative day 1 was greater in patients with postoperative delirium and correlated with delirium severity.[13] The correlation between the elevation of tau and apolipoproteins needs to be elucidated. In addition, among the ApoE isoforms, ApoE2 is the most abundant, and was shown to reduce the risk of progression from mild cognitive impairment to AD conversion by half.[14] ApoE4 had nearly 4 times the hazard ratio for the progression of mild cognitive impairment to AD compared with ApoE2. Therefore, perioperative changes in ApoE isoforms should be investigated further.

Table 2

Logistic regression analysis for pNF-H positivity

	Crude OR	95% CI	*P*	Adjusted OR	95% CI	*P*
log Apo A-I	21.903	1.592–3.165	<.0001	17.579	2.604–118.666	.0024
log Apo B	4.129	2.150–9.862	<.0001	6.057	0.440–83.398	.1709
log Apo E	0.186	0.072–0.420	<.0001	0.032	0.000895–1.145	.0485

Apo = apolipoprotein, CI = confidential interval, OR = odds ratio.

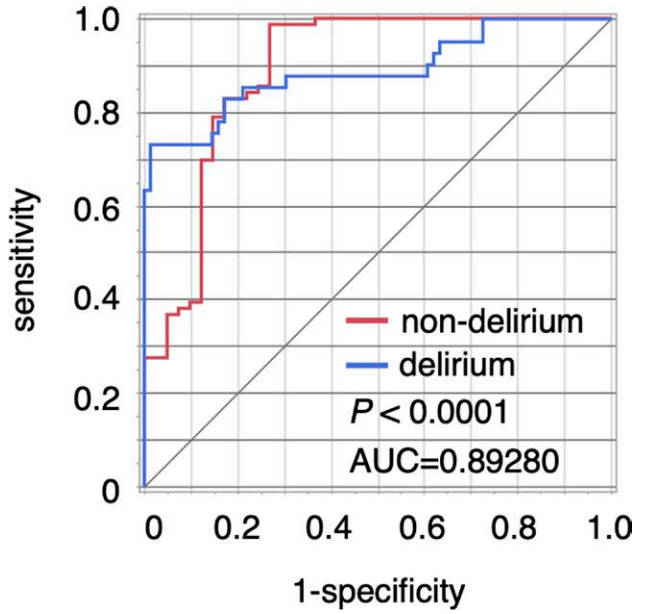

Figure 2. Discriminant analysis using ApoA1 and ApoE as covariates for diagnosing postoperative delirium. (A) Prediction profile for discriminating between delirium and nondelirium with log-transformed values of ApoA-I and ApoE. (B) ROC analysis of the combination of Apo A-I and ApoE to discriminate between delirium and nondelirium patients. Apo = apolipoprotein, AUC = area under the curve.

Another limitation of this study was that patient characteristics including family history of dementia and preoperative presence of cognitive impairment was not explored. It was reported that patients with delirium were significantly more likely to have a positive family history of dementia and preoperative cognitive dysfunction.[13,14] The possibility that these backgrounds can influence on the incidence of delirium and the basal levels of apolipoproteins cannot be excluded. However, we suggest that apolipoproteins can be used to predict delirium even when patient's medical history is unclear.

In conclusion, a combination of ApoA-I and ApoE can be used as an accurate diagnostic biomarker for postoperative delirium, which is highly associated with the presence of pNF-H, a proxy for CNS axonal damage. Serum apolipoprotein might be a therapeutic target to prevent the development of postoperative delirium.

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