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Longitudinal CSF and Blood Biomarkers of Alzheimer’s Disease and Related Dementias Before and After Anesthesia & Surgery

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Background

- Surgery/anesthesia could increase the risk of post-operative cognitive dysfunction (POCD). {Chen CW et al. Alz Dem 2014;10(2); Chen PL, et al. Br J psychiatry 2014}
- Anesthetic drugs and surgical stress may promote amyloid-beta plaque formation, tau phosphorylation and/or neurodegeneration. {Eckenhoff RG, et al. Anesthesiology 2004; Xie Z, et al. Ann Neurol 2008; Planel E, et al. FASEB J 2009; Le Freche H, et al. Anesthesiology 2012; Berger M et al. Annals Clin Trans Neurology 2022}
- Blood-based biomarkers of AD and related dementias (ADRD) provide a more feasible and less costly way to assess ADRD pathological changes versus CSF or PET, but are known to be impacted by renal function, obesity, and other conditions. {Mielke MM et al. Nature Med 2022; Mielke MM & Fowler NR. Nat Rev Neurol 2024}.
- Current evidence is mixed on the effect of anesthesia/surgery on CSF and BBMs of ADRD {Berger M et al, Ann Clin Transl Neurology, 2022; Feinstein I et al, JAMA Neurology, 2021; Wang K et al, BMC Anesthesiol, 2022; Berger M et al, J Alz Dis, 2016; Payne T et al, Br J Anaesth, 2023; Parker M, J Gerontol A Biol Sci Med Sci. 2022; Ballweg T et al, Br J Anaesth, 2021}
- Thus, large studies are needed to determine whether surgery/anesthesia impact change in ADRD CSF and blood biomarkers.

Objective

- To examine pre-surgery, 24-hour, and 6-week post-operative change in CSF and blood ADRD biomarkers among older adults undergoing non-cardiac & non-neurological surgery with anesthesia

Methods

- Adults aged ≥ 60 years undergoing non-cardiac/non-neurologic surgery scheduled for ≥2 hours & previously recruited into the INTUIT, MARBLE studies were included.
 - MARBLE was a randomized, placebo-controlled phase II sequential dose escalation trial (N=203) designed to evaluate the safety of perioperative administration of an ApoE mimetic peptide drug for delirium prevention {VanDusen KW et al. JAD 2020; Timko N, JAMA Netw Open, 2026}
 - INTUIT was an observational prospective cohort study (N=201) of older adults that underwent cognitive testing, collection of blood and CSF, and other questionnaires prior to surgery, and 24 hours and 6 weeks after surgery {Berger M et al. JAGS 2019}
- EDTA Blood and cerebrospinal fluid (CSF) were collected at three timepoints relative to surgery: pre-operative baseline, 24 hours post-operation, and 6 weeks post-operation.
 - Analytes included amyloid-β 1–42 (Aβ42), amyloid-β 1–40 (Aβ40), the ratio of Aβ42/Aβ40, total tau (t-tau, measured only in CSF), phosphorylated tau 181 (pTau181) and 217 (pTau217), and neurofilament light chain (NfL).
- CSF and blood biomarkers were log-transformed and z-scored prior to analyses to compare across uniform units.
- Linear mixed models with a quadratic term for time, when appropriate, were used to examine change in the ADRD biomarkers over the three timepoints.
 - Age, sex, pre-operative estimated glomerular filtration rate (eGFR), BMI, and surgical type were included as covariates.
 - Analyses included all individuals regardless of missing data (all cases) and only those with all three timepoints (complete cases). Results were similar when including cases with missing data, so only the complete cases are shown here.

Results

Table 1. Preoperative Characteristics (N=325)

Characteristic	Median (IQR) / N (%)
Age	68 (65, 72)
Preoperative eGFR	76 (60, 88)
BMI	29.1 (26.0, 33.5)
Male	57.5%
Surgical service	
General	21.3%
Gynecology	5.3%
Orthopedics	37.0%
Otolaryngology	3.4%
Plastic	3.4%
Thoracic	9.7%
Urology	19.7%
APOE4 carrier	28.0%

- Pre-operatively, higher eGFR was associated with significantly lower levels of all plasma biomarkers, but not CSF biomarkers.
- Higher BMI was associated with lower CSF NfL (rho = -0.24, p<0.001) and plasma NfL (rho = -0.25, p<0.001) and with lower CSF pTau217 (rho = -0.16, p=0.004), but not plasma pTau217 (rho = -0.11, p=0.061).

Results, cont

- Among **CSF biomarkers**, there were quadratic time effects across the three timepoints for Aβ40, Aβ42, and total tau such that there were small early post-operative changes (within 24 hours) that resolved by 6 weeks post-surgery.
- Additionally, there was a significant linear time effects for CSF Aβ42/40 ratio such that there was a decline between pre-operative measurement and 6 weeks post-surgery.

Significant quadratic time effects

Significant linear time effects

- Among **plasma biomarkers**, there were quadratic time effects across the three timepoints for NfL and pTau181. Plasma NfL increased most rapidly between pre- and early post-surgery, and continued to increase until 6 weeks. In contrast, plasma pTau181 decreased most rapidly between pre- and early post-surgery and continued to decrease until 6 weeks.
- Additionally, there was a significant linear time effects for plasma Aβ40, Aβ42, and pTau217.

Significant quadratic time effects

Significant linear time effects

Conclusion

- There are small, early post-operative changes (within 24 hours) in CSF AD biomarkers that resolve by 6 wks post-surgery.
- Multiple plasma ADRD biomarkers significantly change from pre- to post-surgery. This is likely a peripheral phenomenon because the changes are not mirrored in CSF.

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