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Editorial

Does Post-Operative Cognitive Decline Promote/Accelerate Alzheimer's disease Pathology? Perioperative Cerebrospinal Fluid Biomarkers and the Gap of Knowledge

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Editorial

A complete definition of neurotoxicity as structural or functional alteration in the nervous system resulting from exposure to a chemical, biological, or physical agent refers to vulnerability of the brain at the extremes of age [1]. The aged brain with a reduced rate of neurogenes is and synaptogenesis is vulnerable to the direct toxic effect of volatile anesthetics [1].

Post-Operative Cognitive Decline (POCD) is a potential consequence of general anesthesia [2]. In a recent prospective multicenter study including 225 patients greater than sixty years of age undergoing total knee and hip replacement, Krenk et al. found that POCD occurred in 9.1% of patients, when tested1-2 weeks after surgery, with an incidence of 8% at 3 months follow up [3]. Concerns over acceleration of cognitive decline following surgical procedures under general anesthesia warrants further investigation into the pathology of Alzheimer's disease (AD) [2]. Although the association between anesthesia and POCD is well documented, the mechanism responsible for this association and progression to dementia has not been determined. A 2009 consensus statement ruled that the benefits of anesthesia may outweigh its potentially toxic effects [4]. Nevertheless, determination of the underlying toxic mechanisms may clarify the etiologies of POCD and AD and create prevention strategies to improve surgical patients' outcomes.

There has been a growth of evidence supporting the use of Cerebrospinal Fluid (CSF) as a diagnostic indicator of neurological disorders, particularly CSF expression of microRNA (miR) and levels of inflammatory cytokines. Increased expression of CSF miR-15b and miR-21 may be diagnostic for glioma [5], Normal Pressure Hydrocephalus (NPH) may cause an increase in CSF TNF-α [6] and patients with Creutzfeldt-Jakob disease (CJD) have been shown to have elevated CSF IL-4 and IL-10 [7].

Currently, the only validated parameter to diagnose AD is the CSF total tau (t-tau) to amyloid-beta1-42 ($A\beta_{1-42}$) ratio [2,8]. Changes in CSF levels of AD biomarkers following anesthesia have previously been studied. A study involving patients undergoing idiopathic nasal CSF leak corrections indicated that total-tau/$A\beta_{1-42}$ ratio increased in a pattern consistent with AD, although this was mainly due to an increase in total-tau. Furthermore, in these patients CSF t-tau was significantly increased at 6-hours post-operatively and remained elevated at 24 hours post-operatively [2]. The CSF t-tau/$A\beta_{1-42}$ ratio exceeded 0.5 at 48 hours post-operatively [2], which is beyond the threshold CSF t-tau/$A\beta_{1-42}$ ratio value of 0.39 for Mild Cognitive Impairment (MCI) [9].

Although total-tau/$A\beta_{1-42}$ is the most valid biomarker, other biomarkers are being studied as well. Zhang et al. found that isoflurane causes an increase in CSF $A\beta_{40}$ levels at 24 hours post-operative [8]. Desflurane has been shown to cause a decrease in CSF $A\beta_{42}$ levels at 2 hours post-operative [8]. However, neither isoflurane nor desflurane caused a significant change in CSF t-tau levels at 2 hours or 24 hours post-operative [8]. These studies show that different biomarkers may be used for different anesthetic regimens and may possibly be used in the future to detect the correlation between cognitive decline and AD.

The results of these two studies present different effects on CSF levels of AD biomarkers following anesthesia. Additionally, neither study provides long-term follow-up on the CSF levels of the AD biomarkers which may provide insight into the progression of AD following anesthesia and surgery. Additionally, there is a growing body of evidence in animal models demonstrating that perioperative hypothermic state may inducte hyperphosphorylation [4,10,11]. Similar findings regarding anesthesia induced hypothermia and tau hyperphosphorylation were published by Planel et al. The authors invite more thorough studies to analyze the effect of anesthesia induced hypothermia on risk and progression to AD [12].

Anesthesia may initiate an acute pro-inflammatory process in the Central Nervous System (CNS) known as neuroinflammation. Tang et al. found that inflammatory biomarkers, interleukin-10 (IL-10), IL-6 and tumor necrosis factor alpha (TNF-α) were all significantly

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elevated in patients' CSF at 24 hours post-operative [2]. Van den Boogaard et al. found that CSF levels of inflammatory markers IL-8, IL-1ra, IL-10 were significantly elevated in delirious patients not suffering from known inflammation [13].

Different types of volatile anesthetics may be responsible for microRNA (miR) expression in the CSF. These changes can potentiate the effects of Aβ without a significant change in Aβlevels [14-16]. Studies done in rats with halothane [14], desflurane [15], and isoflurane[16] showed that a single 3 hour exposure to 1% of the anesthetic gas caused a downregulation of miR-214 expression with accelerated neuronal cytotoxicity of Aβ. This is believed to be attributed to miR-214's function of suppressing BAX, which is lost with the anesthesia-induced down-regulation of miR-214.

Animal model studies demonstrated that upregulation of miR-125b is associated with tau hyperphosphorylation. An increase in miR-125b expression (1.6 fold) was quantified in the prefrontal cortex of AD patients compared to healthy controls [17]. Furthermore, in mice, an upregulation of miR-125b is associated with cognitive deficits similar to those observed in AD patients [17]. Therefore, analyzing the changes in CSF miR-125b following anesthesia may provide insight into pathological tau hyperphosphorylation associated with AD.

A mechanism linking anesthesia with POCD has yet to be determined. Current data shows that following anesthesia, the levels of several CSF biomarkers change. A long term, prospective, observational study analyzing changes in CSF biomarkers and correlating these changes with cognitive function in patients undergoing general anesthesia may provide insight into the pathogenesis of POCD, and possibly AD. Furthermore this data could lead to discovering methods to protect patients undergoing surgery, by preventing the neurotoxic effects of anesthesia.

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