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Does General Anesthesia Promote Alzheimer's disease?

Jennifer Nowak Hauck[1], Niccolo Terrando[2], JasleenKukreja[3] and Marek Brzezinski[2,4]*

[1]Department of Anesthesiology, Duke University, Durham, NC, USA
[2]Department of Anesthesia and Perioperative Care, University of California, San Francisco, CA, USA
[3]Department of Surgery, University of California, San Francisco, CA, USA
[4]Veterans Affairs Medical Center, San Francisco, CA, USA

Introduction

Preclinical studies have revealed that both volatile anesthetics and the surgical stress-related neuro-inflammation are capable of facilitating an Alzheimer's disease (AD)-like neuropathological process [1-7]. We present a comprehensive review of the literature on this controversial topic. The evidence supporting the various mechanisms by which anesthesia and/or surgery may promote AD-like changes will be discussed.

Alzheimer's Disease (AD)

Alzheimer's disease (AD) is the most common form of dementia in elderly people [8].The current disease model of brain pathology underlying AD is characterized by accumulation of β amyloid plaques and tau tangles, which account for synaptic loss and dysfunction, neurodegeneration, and a decrease in brain size [8]. Typically, the symptoms of mild cognitive impairment (MCI) or dementia lag behind AD pathology by many years, i.e., many patients have the neuropathological substrate of β amyloid without signs or symptoms of cognitive impairment. This process can span over decades and include multiple stages: preclinical (no complaints or impairments), mild cognitive impairment, and dementia [8,9]. Clinically, the patient presents with memory loss, general cognitive decline, and as the final step, dementia. The majority of cases of AD are late-onset and sporadic in origin [10,11]. While risk factors for the development of AD, including advanced age, tobacco use, and presence of the apolipoprotein (ApoE) ε4 status allele have been identified, none has been found to reliably predict AD in individual subjects [12-14]. Since AD is a neurodegenerative disorder, it can only be diagnosed with a post-mortem neuropathological examination, revealing plaques composed of extracellular aggregates of the β -amyloid peptide and intracellular neurofibrillary tangles composed of hyper phosphorylated tau protein [8]. Clinically, the diagnosis can be made with evidence of memory impairment and at least one other cognitive disturbance (aphasia, apraxia, agnosia or executive dysfunction), a significant decline from premorbid level, and a gradual onset with progressive course [15-17].

Postoperative Cognitive Dysfunction (POCD)

Postoperative Cognitive Dysfunction (POCD) is a form of cognitive decline that may occurs after any operation, but is particularly common following cardiac and orthopedic procedures [18-21]. POCD is characterized by impairment of memory, learning difficulties, and reduced ability to concentrate after surgery [19,22-26]. POCD can be classified as acute (weeks), intermediate (months), and long-term (years) by timing of occurrence of cognitive decline after the operation [22,24,27-30]. The first adequately powered study of POCD was conducted by Moller and colleagues in 1998, who studied 1218 patients ages 60 and older scheduled for elective non-cardiac surgery [26]. The salient finding of the study was that 27% and 10% of patients were found to develop POCD at 1 week (early POCD) and at 3 months (late POCD) after surgery, respectively. Factors associated with development of early POCD included increasing age, prolonged exposure to anesthesia, poor education, post-op infections and respiratory complications [26]. Since this landmark publication there has been a plethora of studies examining this area suggesting that up to 50% of surgical patients suffer from POCD in the early weeks following a major non-cardiac surgery [13-19]. Although cognitive performance gradually improves over time in the majority of patients with POCD, with an incidence of 10-14% at 3 months and 1% at one year after surgery [22,24,26,28,29], permanent cognitive decline after surgery has been described [24]. Clouding the picture is the fact that POCD does not have universally accepted diagnostic criteria, as multiple neuropsychological battery of tests with various cutoff scores as well as varying post-surgical time-points for assessment are used in diagnosis [19,22,24,28,31-35]. This problem was highlighted by Newman et al. who reported in their comprehensive review of POCD in non-cardiac surgery that the timing of the first postoperative assessment of cognition varied between few days to approximately 1 year after surgery [22]. Some studies conducted multiple follow up assessments whereas others only used one [22]. Some defined POCD as a decrease in performance equal to or greater than 1 SD from pre-operative performance on 2 or more tests [36] whereas other studies required 1 SD decline in anywhere from one test to 20% of the tests [37,38]. Some of them used results of multiple neuropsychological tests to produce a single score while others used multiple scores. Finally, Newman et al. calculated that 70 different neuropsychological tests have been used in the studies reviewed [22]. The fact that some studies failed to evaluate baseline cognitive function prior to surgery and only examined cognitive function after surgery while other evaluated the baseline function anywhere from 1 day to several years before surgery [39] adds another layer of complexity to a better understanding of POCD [19,22]. The lack of universally accepted diagnostic criteria and varying post-surgical time-points for assessment has been highlighted in the recent review of POCD following cardiac surgery [19].

Does Surgery and Anesthesia Promote AD Neuropathology?

Multiple peri operative factors including volatile anesthetics, surgical stress-related neuro inflammation, hypoxia, hypocapnia, and isch-

***Corresponding author:** Marek Brzezinski, M.D., Ph.D., Anesthesiology Service (129), Veterans Affairs Medical Center, 4150 Clement Street, San Francisco, CA 94121, Tel: (415) 750-2069; Fax: (415) 750-6653; E-mail: brzezinm@anesthesia.ucsf.edu

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emia, have been suggested to induce and promote AD-neuropathology and lead to postoperative cognitive dysfunction [6,40].

Pre-clinical studies

Volatile anesthetics: Multiple recent studies explored mechanisms by which anesthetics may promote AD, including apoptosis, caspase activation, AB oligomerization, tau hyperphosphorylation, and TNF-alpha release [2,5,41-50]. The effects of anesthetics on protein expression and long-term potentiation in the hippocampus, an area of the cortex highly indicated in AD pathology, have been of particular interest. In a murine model, Xie et al, showed that the inhalational anesthetic, sevoflurane, induces apoptosis and elevates levels of β amyloid [41]. Similar results were found with isoflurane, another commonly used inhalational anesthetic [42,44]. Interestingly, AD transgenic mice showed a greater degree of neurotoxicity as compared to naïve mice when exposed to sevoflurane, suggesting that brain with AD-neuropathology may be more vulnerableto inhalation anesthetics [51]. Administration of inhalational anesthetics was also associated with functional decline which is normally found in AD [45,52]. Isoflurane administration to wild-type rats and mice produced prolonged decrease in memory and learning [45,52]. Lu and colleagues who examined the effect of sevoflurane on caspase activation in brains of naïve neonatal mice and neonatal AD transgenic mice [51] reported a significant increase in caspase activation in both naïve mice and AD transgenic mice when compared to controls. Disconcertingly, this increase was significantly greater in the AD mice [51]. In contrast, in vitro studies using human cortical neuron cellfailed to demonstrate an increase in expression of caspase 3 with clinically relevant concentrations of volatile anesthetics (including sevoflurane, isoflurane and desflurane) [53].

Halothane and isoflurane have been found to enhance amyloid β oligomerization [54,55] by lowering the amyloid β concentration necessary to initiate oligomer formation [55]. These results caution against using inhalational anesthetics in patients with preexistent levels of brain β amyloid, like in patients with AD [41]. It should be noted, however, thatethanol and propofol were found to modestly enhance oligomerizationas well [54].

Growing literature suggests that volatile anesthetics decrease synaptic plasticity in the hippocampus by impairing long-term potentiation in the murine hippocampus [56,57]. Finally, exposure to 1 MAC isoflurane for 3 hours was associated with a significant up or down-regulation of hippocampal proteins that have also been shown to play a role in AD pathology [58].

Perioperative neuro inflammation: Since inflammatory process including activated microglia and elevated levels of pro-inflammatory mediators (e.g., cytokines) has been implicated in the process of β- amyloid accumulation in AD [59-63], the effects of surgery-induced neuroinflammation on AD neuropathology has been an area of research [2,47,48,64-68]. Hu and colleagues were one of the first to propose that the systemic inflammatory response to surgical stress and not the anesthetic agents is the link between POCD and AD [1]. They suggest that peripheral inflammatory cytokines released during surgery enter the blood brain barrier, and subsequently activate microglia cells and vascular endothelial cells to release various inflammatory mediators. Furthermore, surgical stress induces a neuro inflammatory response which also activates microglial and vascular endothelial cells [3,4,67-69]. These inflammatory mediators contribute to cognitive decline by influencing the production and effects of neurotransmitters, neuroplasticity, and neurotoxicity [3,4,67-69]. Parenthetically, surgery-related inflammation and inhalational anesthetics, isoflurane in particular, increase the permeability of the blood-brain barrier thus possibly mediating the entry of inflammatory cytokines into the brain [48,70,71]. The permeability of the blood-brain barrier in a murine animal model wasreported to be affected by nociceptive signaling as well [72]. In a landmark study, Wan and colleagues used a rat animal model to examine whether a surgical procedure can trigger a pro-inflammatory cytokine response in the hippocampus and whether such an inflammatory response is associated with cognitive dysfunction [3]. The animals were randomly assigned to one of the three groups: naïve controls, anesthesia without surgery, and anesthesia with surgery (splenectomy). The animals were anesthetized with fentanyl and droperidol. Consistent with their original hypothesis, anesthesia alone was not associated with cognitive decline as compared to control rats [3]. There was, however, a significant cognitive impairment on postoperative day one and three in splenectomized rats when compared to control rats. A corresponding glial activation in the hippocampus suggesting neuroinflammation in splenectomized rats was seen on day one and three. Similarly, other animal models of surgery-induced cognitive decline (orthopedic surgery, hepatectomy, minor abdominal surgery) have been described in associating surgical trauma with memory dysfunction and pathogenic hallmarks in rodents [67,68,73,74]. These results point toward surgical trauma-related neuroinflammation as the pivotal mechanism underlying POCD [3].

Other factors: Anesthesia can impair normal thermoregulatory control [75]. Planel and colleagues examined the possibility that general anesthetics promote AD-neuropathology by inducing hypothermia. They found that anesthetic-induced hypothermia leads to rapid and robust tau hyperphosphorylation in the brain of normal mice after 1 hour of exposure, regardless of the anesthetic used (chloryl hydrate, pentobarbital sodium, isoflurane) [76]. Further, once normothermia was achieved the tau hyperphosphorylation was completely reversed; leading to the conclusion that tau hyperphosphorylation was secondary to anesthetic-induced hypothermia and not due to the anesthetic itself. These effects of anesthetic-induced hypothermia on tau-phosphorylation, solubility, and function were later confirmed in mice expressing a tau mutation that causes frontal-temporal lobe dementia, suggesting that patients with preexistent AD may be at risk of disease progression when exposed to perioperative hypothermia [77].

Hypoxia and hypocapniahave also were examined [6] as promoters of AD pathology. Xie and colleagues exposed human neuroglioma cells to hypocapneic conditions (PCO_2<40 mmHg) or hypocapneic plus hypoxic (>21% oxygen) conditions and found that hypocapnia induced caspase-3 activation and apoptosis. Hypoxia combined with hypocapniainduced apoptosis in a synergistic manner. Hypoxia alone did not increase caspase-3 activity [75]. The same group reported that the inhalational anesthetic, Desflurane, promotedapoptosis when administered under hypoxic condition [5]. Desflurane (12%) and hypoxia when applied alone failed to induce these changes [5]. Finally, mild and severe brain ischemia, frequently encountered intra-operatively in older patients, has been found to increase β amyloid deposits in animal models of ischemia and in postmortem human AD brain [6,78-81].

Human studies

In contrast to a plethora of animal studies suggesting a connection between exposure to surgery and anesthesia and development of AD-neuropathology, there is currently only limited evidence to support such a relationship in humans. Gasparini and colleagues examined the hospital records of 115 patients with probable AD based on a clinical diagnosis [82]. Each of these patients was age and sex-matched with 2 patients with non-degenerative neurological diseases and 2 pa-

tients with Parkinson's disease. Records were reviewed for exposure to anesthesia in at least 1 year but no greater than 5 years before their diagnosis of AD. No association between AD and exposure to anesthesia in these preceding years was found. There was also no association found between number of surgical procedures and development of AD. Since patients with AD were significantly older at the time they underwent surgery, the authors concluded that older age represents a risk factor for development of POCD [82]. Avidanet et al. [39] reviewed retrospectively the records of 214 non-demented and 361 of mildly demented (Alzheimer's-type) patients, and divided them in one of three groups: history of non-cardiac surgery, major illness, or control group. All patients had at least one thorough baseline cognitive function test and underwent annual clinical assessments and psychometric testing. The cognitive function declined more rapidly in demented patients than non-demented patients regardless of whether they had non-cardiac surgery, a major illness, or neither [39]. The progression of non-demented patientsto dementia was not related to non-cardiac surgery or a major illness. Progression to dementia was, however, predicted by older age. The authors concluded that non-cardiac surgery was not associated with an increased rate of progression of disease in those already diagnosed with dementia nor was it associated with new development of dementia [39]. In a large retrospective case-control study Zuo and colleagues attempted to determine whether spine surgery under general anesthesia and anesthetic choice contributed to AD development [83]. Researchers followed 10,000 patients who underwent spinal surgery over a 12-year period. They identified 26 of these patients that developed AD and 161 control patients who had spinal surgery but did not develop AD after the surgery. No difference in gender, length of operation, length of hospital stay, or type of anesthetic was found between the groups [83]. The only significant difference was age of the two groups: patients who developed AD were significantly older than patients who did not.

Growing evidence points towards reduced brain reserves [84] as a risk for developing of POCD. Bekker and co-workers who examined the impact of preoperative cognition on postoperative cognitive function, found preexistent Mild Cognitive Impairment to be a risk factor for developing postoperative cognitive decline [85,86]. Lower educational level was also reported to be a risk factor for development of POCD [25].

Evered et al. examined the relationship between preoperative plasma biomarkers for AD Aβ42 and Aβ40 and postoperative cognition in 332 patients scheduled for CABG [87]. Blood levels of Aβ40 and Aβ42 peptides are thought to have diagnostic and predictive value in the evolution of AD [88], with lower plasma levels of Aβ42 and Aβ40 related to deposition of β amyloid in the brain, indicating preclinical stage of AD [88]. This study found significantly lower levels of preoperative plasma Aβ42 and Aβ40 in patients who developed postoperative cognitive decline, providing further evidence linking postoperative cognitive decline with preclinical AD [88]. A robust neuroinflammatory response in the CSF in the perioperative period, including interleukin-6, tumor necrosis factor alpha, interleukin-10, S100Beta, and tau, has been confirmed by other groups as well [89].

Summary

Does anesthesia and surgery promote AD? The data in humans is still too limited to reach a firm conclusion in this causal relationship. Repetitive exposure to anesthetics has not been associated with cognitive decline in population studies [28,39,90-93] and the use of volatile anesthesia has been characterized by an excellent safety record [94]. Having said that, the inverse correlation between the cumulative exposure to general and spinal anesthesia before the age of 50and the onset of AD seem to support the hypothesis that anesthesia and surgery promote AD [64]. Finally, it is not clear whether patients with POCD are at higher risk for subsequent development of AD.

Collectively, the available preclinical results raise concern that anesthetic agents and the surgical trauma-related neuroinflammation may interact with the established pathways of neurodegeneration, leading to increased neurotoxicity, and promote/accelerate AD pathology. Preexistent AD pathology may be associated with increased vulnerability to both processes and increase risk for postoperative cognitive decline. Some suggested that patients with preexistent β amyloid deposits could be at risk for AD acceleration with general anesthesia and postoperative cognitive decline [64,95]. While the clinical evidence is insufficient to consider changing the current use of volatile anesthetics in anesthesia, the evidence suggesting the possible role of hypoxia, hypocapnea and hypothermia in cognitive decline should guide clinicians to more tightly regulate these parameters in elderly patients.

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