Anesthesia and Alzheimer’s: A review

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Abstract

As early as 1955, it was Bedford who provided description of cognitive changes in elderly patients following anesthesia and surgery. Reports of individuals with catastrophic, non-stroke-related decline in cognitive functions following anesthesia and surgery lead to a perception in the lay population that anesthesia and surgery have the potential to greatly exaggerate the progression of dementia, particularly Alzheimer’s disease (AD). There is a concern that anesthesia and surgery could cause irreversible impairment, leading to AD. This could also explain the accelerated decline in patients with mild cognitive impairment. We seek to explore the relevant literature to determine whether a correlation exists and then propose a possible pathophysiologic mechanism.

Keywords: Alzheimer’s disease, anesthesia, biomarkers, mild cognitive impairment, regional

Introduction

Alzheimer’s Disease (AD) is the most common form of dementia characterized by severe neurodegeneration, neuroinflammation, and the progressive loss of cognitive abilities.\(^1,2\) It is estimated that 5.1 million Americans are living with AD, which equates to 13% of adults over the age of 65. Due to changes in demographics and an increasing life expectancy, these numbers are expected to increase to over 7.7 million by 2030.\(^3,4\) For patients, the effects of AD are debilitating and life altering, with AD being the leading cause of admission to long-term care facilities. A total of 8.5 billion hours of caregiver time and a current annual cost of 148 billion dollars is spent caring for patients with AD.\(^3\)

Given these numbers, it is increasingly likely that anesthesiologists will encounter patients with AD in the OR. As anesthesiologists, it is important to stay current with changing medical trends in order to provide the best care for our patients. It is unclear what the precise cause and pathogenesis of AD is, but recent reports have shown a growing interest in a potential link between exposure to anesthetic and the progression of AD.\(^1\) Currently, there is discussion as to the validity of this correlation. As anesthesiologists, not only is it important that we understand this disease to provide care for our patients, but also stay current in the trends that encompass our field. This review hopes to address the medical considerations for this growing population who will be undergoing surgery to make sure they receive the best possible care.

History

In 1955, the first documented description of cognitive changes in elderly patients following anesthesia and surgery was reported in a retrospective review of 1193 patients. Ten percent of these patients experienced transient, mild cognitive problems of concentration and function. However, in 1.5% of these patients, extreme dementia and confusion remained until death.\(^5,6\) Since then, the definitions of what is cognitive change following anesthesia have been elaborated upon into...
the diagnosis of postoperative cognitive dysfunction (POCD), which manifest as new cognitive deficits that arise immediately after surgery and generally are reversible in days to months. This differs from dementia, which is severe impaired memory and abstract thinking that develops progressively over months to years. While POCD is an accepted reaction to anesthesia, there is no accepted consensus that anesthesia is a risk factor for dementia. However, new individual reports of catastrophic, non-stroke related declines in cognitive function following anesthesia have created a concern that anesthesia and surgery could cause irreversible cognitive impairment which can either accelerate a progressive decline of dementia or induce the brain pathology of AD in healthy individuals.\[11\]

Adverse neurological events have been documented in pediatric patients exposed to general anesthetic as well under the term anesthetic-induced developmental neurotoxicity. The perceived mechanism involves apoptosis of the gamma-aminobutyric acid (GABA)-ergic and glutaminergic neurons prior to synaptogenesis is completed through free radical production.\[7\] A major prospective study by the Pediatric Anesthesia Neuro Development Assessment in pediatric patients undergoing inguinal hernia repair with their healthy siblings as a control showed that neurocognitive, behavior, and intelligence quotient score outcomes were not statistically different between the two in later childhood.\[8\] The later general anesthesia and awake-regional anesthesia in infancy (GAS) trial which compared infants receiving wake-regional anesthesia versus GA also found no increase in adverse neurological outcome in later childhood.\[9\] The most recent Mayo Anesthesia Safety in Kids study which investigated the effects that multiple anesthetics have on neurocognitive performance also showed anesthetic exposure was not associated with general intelligence deficits. The secondary outcomes of the study may suggest that multiple exposures to GA may be associated with a pattern of changes associated with learning difficulty.\[10\] The recent interest in studying an association with anesthetic exposure and cognitive decline in the young and elderly is exciting and may represent a possible link between the mechanism behind both of these phenomena.

Pathophysiology and genetics

The pathological hallmarks of AD include senile plaques consisting of beta-amyloid as well as defibrillation tangles consisting of hyperparathyroidism tau.\[1,3\] The amyloid protein plaques arise early in the disease, approximately 10–20 years before the onset of symptoms. The accumulation of this naturally present peptide is thought to be the cause of neuron degeneration. Studies have demonstrated that there is degeneration of the cholinergic neurons originating from the basal forebrain nuclei that project to the cerebral cortex.\[11,12\] It is believed that this loss of cholinergic neurons is responsible for some of the learning and memory deficits seen with this disease, and may explain why acetylcholinesterase inhibitor medication can be used to treat some of the symptoms of AD. Tau is a protein found in the neuron axon that stabilizes the microtubules required for protein function and polymerization. When tau becomes phosphorylated, its affinity toward microtubules decreased which promotes the formation of neurofibrillary tangles (NFTs). The presence of NFTs is more highly correlated with the clinical alternations in dementia than that of amyloid plaque.\[13\]

While there is no definitive cause of AD, several isolated risk factors include advanced age, female gender, low educational achievement, family history, a history of head trauma, cardiovascular risk factors, and specific genetic mutations.\[14\] The main isolated genetic mutations associated with AD are mutation in the presenelin 1 and presenelin 2, which account for 70% and 20–25% of the cases of early onset AD, respectively.\[3\] The inheritance of certain polymorphisms of Apolipoprotein E (ApoE4) has also been implicated in the common forms of AD. Inheritance of ApoE4 increases the risk and lowers the age on onset of AD. ApoE2 actually lowers the risk and increases the age of onset.\[3,15\]

Background on anesthesia

The anesthetic medications used in general anesthesia can be divided into inhalational and intravenous agents. Inhalational agents are halogenated hydrocarbons or ethers that are administered into the pulmonary system through the anesthesia machine in precise concentrations in combination with air, oxygen, and sometimes nitrous oxide.\[1\] Both types of agents are lipid soluble, cross cellular membranes easily, and enter the brain readily.\[3\] The molecules act on multiple receptors including ion channels, second messenger systems, and cytoskeletal components.\[16\] For many years, these agents were assumed to be nontoxic and reversible. The appearance of in vitro studies which suggest these anesthetics may have neurotoxic effects in vulnerable populations such as the elderly have prompted further research and new hypotheses into the mechanism of effect for these medications.

Many hypotheses have been proposed explaining the link between exposure to anesthetics and AD including a potential neurotoxic effect of the inhaled anesthetic caused by increased production of beta amyloid through acceleration of neurodegenerative mechanisms, increased phosphorylation of tau protein, and increased neuroinflammation.\[12\] It has also been suggested that the trauma of surgery itself may play a role in the development of AD, irrespective of anesthesia.
Biochemical, cell culture, and animal studies
The idea of an interaction between anesthetic agents and AD pathology was first reported by Eckenhoff using the biochemical experiments of light scattering, thioflavin binding, and analytical centrifugation. His group found that the solubility of amyloid beta decreased when exposed to the commonly administered inhalational anesthetics desflurane and isoflurane as well as intravenous anesthetic propofol. Decreased solubility of amyloid beta lead to an increase in plaque formation.[17,18] Additional NMR studies suggested a potential interaction site within the amyloid beta monomer for the anesthetic propofol on certain critical residues.[19] Interestingly, some anesthetics appear to enhance A-beta oligomerization in a synergistic way. Intravenous diazepam did not induce A beta peptide oligomerization alone, but when co-administered with halothane in clinically relevant concentrations it did induce oligomerization.[19]

Mouse hippocampus neurons and Human neuroglioma cells exposed to inhalational anesthetics including isoflurane and sevoflurane were also associated with increases in beta-amyloid and the induction of apoptosis.[20,21] Using flow cytometry and immunocytochemistry, researchers found an increased level of reactive oxygen species (ROS), increased level of the proapoptotic factor Bax along with decreased levels of the antiapoptotic factor BCL-2, and opening of the mitochondrial permeability transition pore (mPTP). These findings together suggest a potential mechanism in which anesthetics promote mitochondrial instability and apoptosis through activation of caspase-3.[22] When exposed to cyclosporin A, a mPTP opener blocker, the effect of caspase 3 activation was attenuated, further supporting the hypothesis of mitochondrial instability.[22]

Animal models looking at 4–6-month old mice that were exposed to inhalational anesthetics found a massive and rapid induction of tau hyperphosphorylation. The mechanism was not a result of anesthesia directly, but through anesthesia-induced hypothermia leading to inhibition of protein phosphatase 2A (PP2A). Return to normothermia during anesthesia leads to a return of tau phosphorylation to normal levels.[23-25] Further studies have shown that a 1-h exposure to intravenous propofol was also found to be associated with tau hyperphosphorylation even under normothermic conditions from an unknown mechanism.[26]

In vitro mice studies comparing wild type and transgenic mice with an A-betaPP expression mutation showed that exposure to the inhalational anesthetics isoflurane and halothane resulted in decreases in cognitive performance and reduced exploratory behavior.[27] On autopsy, the transgenic mice had increased levels of apoptotic cells, increased A-beta aggregates, reduced autophagy, reduced astroglia, and increased microglial responses while the WT animals were not affected.[28] Additional mouse studies separating acute and chronic administration of inhaled anesthetic showed that acute exposure leads to a dose-dependent but reversible increase in hippocampal tau phosphorylation. Chronic exposure leads to significant memory impairment on Morris water maze evaluation and persistent tau hyperphosphorylation.[29]

The issue of a potential confounding factor of surgery itself being a potential causative factor in the link between AD and anesthesia was explored in mouse models which subjected anesthetized rats to splenectomy versus no surgery. The splenectomized rats had a period of cognitive dysfunction assessed by performance in Y-maze as well as hippocampal glial cell activation and inflammation when compared to the control who only received anesthesia.[30] Another study comparing partial hepatectomized mice under general anesthesia also showed memory impairment on Morris Water Maze performance, gliosis, A-beta accumulation, and tau protein phosphorylation when compared to controls exposed to anesthetic and fentanyl. The controls show none of the changes in maze performance or inflammatory markers.[31] An additional study comparing triple transgenic AD mice to WT mice who both underwent cecal ligation and desflurane anesthetic resulted in cognitive impairment persisting to 14 weeks, microglial activation, amyloidopathy, and tauopathy. In WT mice, there were no differences between the surgery, anesthetic, or air controls.[32]

The current literature composed of biochemical, cell culture, and mouse model studies agree with the hypotheses that anesthesia induces the pathophysiology of AD through oligomerization of A-beta and hyperphosphorylation of tau. Surgery has also been shown to possibly have an independent effect on these pathways.

Intraoperative biomarkers for dementia
Classically, AD is a clinical diagnosis which requires a combination of criteria involving medical history, cognitive testing, and neurological examination to diagnose. Imaging modalities such as MRI can be used to rule out other causes of dementia but is inadequate alone. Unfortunately, the development of AD has a long refractory period where pathology can develop in the absence of detectable symptoms.[33] There are few blood biomarkers agreed upon for diagnosis of AD. In recent years, inflammatory markers, soluble A-beta, and tau have been proposed as biomarkers to detect the presence of AD in patients who lack the clinical signs or symptoms.[4]

Current literature reveal potential cerebrospinal fluid (CSF) biomarkers related to the main pathologic features present in
AD, the oligomerization of A-beta and hyperphosphorylation of tau. The AB1-42 is an amyloid peptide composed of 42 amino acids which makes it highly insoluble and readily able to oligomerize into extracellular A-beta deposits. AD is associated with a decreased CSF AB1-42 level. Tau can be found as a protein present in the cytosol of neurons which becomes hyperphosphorylated in AD. After phosphorylation, the protein detaches from microtubules and accumulates in the form of NFTs, resulting in increased CSF phosphorylated tau 181 (P-tau181) as well as total tau protein (T-tau). By using a combination of these values, studies reached diagnostic power to discriminate between AD and cognitively healthy controls with sensitivity and specificity reaching 92 and 89%.34,35

Researchers conducted a study to see if the levels of the combined biomarker CSF t-tau to AB ratio changed during, before, and after surgery with inhalational anesthesia or surgery with total intravenous anesthesia (TIVA). A lumbar drain was administered at the time of surgery and CSF aliquots were drawn at baseline, at the end of surgery, and 6, 24, and 48 h after surgery. Results showed that changes in CSF A-beta 1-42 were statistically insignificant throughout the 24-h postoperative period. Total tau was significantly increased after 6 h and more than 200% increased after 24 h, with a T-tau to A-beta (1-42) exceeding 0.5 at 48 h after surgery.33

While the current studies using biomarkers to quantify the effect anesthesia has on dementia biomarkers are new, their preliminary results show promise in that these biomarkers can be used to show a convincing trend that may explain how anesthetics can be associated to AD.

**Human studies**

Currently, retrospective studies evaluating the association between general anesthesia and dementia have yielded results inconsistent with the results found in preliminary biochemical and animal studies. The largest systematic review of the data which analyzed 15 case-control studies found no association between exposure to GA and risk of AD (pooled OR: 1.05; 95% CI: 0.93-1.19, P = 0.43).3 Subgroup analysis comparing general anesthesia to regional anesthesia was also statistically insignificant nor was there a statistically significant association between the number of surgeries involving GA exposed to and AD.3 Other case-control studies have found no associated risk between the number of surgical operations and AD.36

In the current literature, high powered prospective studies looking at the association between AD and anesthesia are rare. This can be due to the difficulty of setting up a protocol with an observation period long enough to detect the development of AD given its long refractory period with an absence of symptoms. The latest prospective cohort study by Bowles focusing on a group of 3,988 participants based in Seattle of 65-year old or older, dementia free individuals. Researchers used surveys to generate data on dates of exposure to surgery and anesthesia, as well as types of anesthetic for an average follow-up of 7 years prior to the development of any dementia or AD.37 From this group, 24% were diagnosed with dementia and 19% with AD. There was no statistically significant association between high-risk surgery with GA and developing dementia (HR = 0.86, 95%CI = 0.58–1.29) or AD (HR = 0.95, 95%CI = 0.61–1.49) compared to those with no history of GA. Interestingly, those with any history of any surgery with GA were found to have a lower risk of developing dementia (HR = 0.63, 95% CI = 0.46–0.85) and AD (HR = 0.65, 95%CI = 0.46–0.93) compared to those with no history of exposure to GA.37 While both groups receiving surgery and GA showed no increased risk of developing dementia or AD, comparing the high-risk surgery with GA to any surgery with GA group found a HR of 1.37 (95% CI = 1.04–1.80) for dementia and 1.46 (95% CI = 1.07–1.99) for AD, consistent with hypothesis that high-risk surgery adds additional stress, leading to delirium and subsequent dementia or AD. Underlying medical conditions contributing to the need for high-risk surgery may confound the association.

To date, this study is one of the largest population-based studies on anesthesia exposure to evaluate the association between GA and AD. A major limitation of the study includes exposure data collected using a self-reporting system as opposed to confirmed medical records, opening the possibility of recall bias. While this major study provides much information against the perception that anesthesia increases the risk of AD, further studies will be required to gain enough evidence on what to do in the face of conflicting preliminary studies.

**Discussion**

While the perception that exposure to GA is an increased risk for AD has sparked relatively recent attention, there is a respectable amount of data on detailing the issue. Preliminary biochemical studies have been consistently shown both inhalational and intravenous anesthetic produce effects similar to the pathogenesis of AD. Researchers have found anesthetics increase oligomerization of beta-amyloid and neuronal death through a proposed mechanism involving caspase-3 activation.20,22 Other cell culture and animal studies have also shown that anesthetic promotes hyperphosphorylation and destabilization of tau protein from microtubules through...
inhibition of PP2A. This mechanism may or may not be related to hypothermia induced by anesthetic.

It is important to remember AD is a clinical diagnosis with many manifestations, pathology only being one of them. When analyzing the data that exist in humans, the connection between anesthetic and AD pathogenesis becomes less clear. The majority of high-quality studies analyzed through systemic review indicate no significant association between anesthesia and the development of AD. These studies were high-quality case-control studies using standardized Newcastle–Ottawa Criteria. The latest recent large scale, prospective cohort study also shows a history of surgery with GA or even high-risk surgery with GA predisposed people to dementia or AD. In fact, surgery with GA was a statistically significant protective factor against AD. This may be due to the fact that these patients receiving at least one surgery indicate they well connected to the health system, receiving care, and at overall higher baseline health compared to other cohorts who have never received surgery or instead received high-risk surgery.

With all of these studies, it is important to remember the limitations in study design. The development of AD has a long and variable refractory period where patients exhibit no detectable symptoms which would make studies with shorter follow-up likely to underestimate those with AD. Furthermore, due to the innate connection between GA and surgery, it can be difficult to separate the effects of both on outcomes. Mouse models have shown there are lasting effects on cognition and pathological changes from surgery alone, but it would be unethical to study this on humans. Human studies exploring this issue by comparing the effects from high-risk surgery to that of any surgery expose both groups to anesthetic, adding further confounders.

The lack of validated blood biomarkers makes it difficult to come up with a reliable and reproducible standard for diagnosis. The use of CSF A-beta1-42, t-tau, and p-tau181 have been shown to have diagnostic value for Alzheimer’s disease. However, this has mainly been validated through research and yet to be validated in clinical practice. Currently many groups push for the development of automated immunoassay methods according to specific protocol in the clinical space. A recent study investigating the issue using these biomarkers have shown positive results, with biomarkers consistent with neuronal injury and AD pathogenesis taken 48 h after surgery.

Due to the limited power and time period assessed in this study, it is difficult to ascertain whether or not the increasing trend in biomarker level is related to acute, reversible neurological stress or if they do correspond to the pathogenesis of AD.

However, the introduction of human trials that incorporate the use of newly developed biomarkers to investigate the link between GA and AD is an exciting new step in this field. The need for obtaining CSF makes larger studies logistically difficult, but not impossible. A future clinical trial that compares the short- and long-term CSF biomarker changes using intermittent lumbar punctures at longer time periods would be an interesting clue to this development.

However, given the current level of evidence and studies showing that anesthetic administered at clinically relevant doses do not increase likelihood of causing neurotoxicity or neurodegenerative disease in human populations, it appears premature to alter clinical practice. The ultimate goal should continue, and one should not compromise the goals of patient safety, comfort, and optimal conditions for surgery until further clinical data is generated. However, given the positive results, it appears to make sense to use the lowest reasonable effective dose and concentration of anesthetic required for each individual patient’s needs.

Conclusion

The recent perception that GA may have unknown neurotoxic effects and potentially correspond to developing neurodegenerative disorders like AD is not new. A bevy of studies and information provide differing and inconclusive evidence. New developments in the field of biomarker data and prospective human trials will hopefully provide enough information to make an informed decision in the future.

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Conflicts of interest
There are no conflicts of interest.

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