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Postoperative cognitive dysfunction, Alzheimer's disease, and anesthesia

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Although aging itself is not a disease, there are many comorbidities that become more common with aging. Heart disease, cancer, and other chronic illnesses are either more common or more severe in aging patients. Approximately 5.5 million people in the United States have Alzheimer's disease (AD), with the principal risk factor being age. It is estimated that the incidence of AD diagnosis doubles every 5 years after the age of 65 [1]. Therefore, as the population ages, the impact of AD on the healthcare landscape will increase. Understanding how to manage patients with AD is critical as we begin to care for more elderly patients in the perioperative period [2]. In addition to their other health considerations, aging surgical patients are increasingly more likely to have pre-existing AD or be at risk for developing AD. There is growing interest to determine how anesthesia affects the development or progression of AD. Similarly, a best practice for the anesthetic management of patients with AD is not yet defined. Finally, the relationship between AD and susceptibility to or exacerbation of postoperative cognitive dysfunction (POCD) is not well understood. In this review, we will discuss both the clinical and the preclinical data related to anesthesia and AD, describe the overlapping pathophysiology of neurodegeneration and provide some insight into the anesthetic care of patients with AD.

KEYWORDS: anesthesia, elderly, Alzheimer's disease

Introduction

There is ongoing public concern about cognitive decline as a result of surgery and/or anesthesia [3]. The potential for surgical anesthesia to exacerbate neurodegeneration is a controversial topic which affects not only patients but surgeons, anesthesiologists, and third-party payers in the health care industry. Each of these stakeholders have a unique perspective on surgical anesthesia which will be difficult to separate from their potential gains/losses if policy or reimbursement changes become based on critical evidence related to this topic. Although resolution of this complex situation is beyond the scope of any single publication, this review seeks to define perioperative central nervous system (CNS) complications typical of patients with Alzheimer's disease (AD) in the context of known neuropharmacological mechanisms and to discuss what is known and what is not known about the more ill-defined postoperative cognitive dysfunction (POCD). Using the most relevant articles in the literature that focus on mechanisms known to be affected by anesthesia drugs, this review (1) defines AD and POCD, (2) discusses both the preclinical and clinical data related to anesthesia and AD, and (3) provides some insight into the anesthetic care of patients with AD.

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Alzheimer's Disease and Postoperative Cognitive Dysfunction—Defined

Alzheimer's disease is a progressive, age-related neurodegenerative disease that leads to cognitive decline. Although many mechanisms have been identified in the pathophysiology of AD, the core disturbance is abnormal protein folding that leads to oxidative stress, inflammatory damage, and synaptic dysfunction [4, 5]. Two major proteins, β-amyloid peptide (Aβ peptides) and tau, are implicated in the pathogenesis of AD. Aβ peptides are normal products of metabolism, however, there is an imbalance between production and clearance in AD where Aβ accumulate and aggregate into neuritic plaques and neurofibrillary tangles in temporal-lobe structures. Tau also forms neurofibrillary tangles

in AD. Tau promotes assembly and stability of microtubules and vesicle transport. In AD, it is hyperphosphorylated, leading to less degradation of the protein and abnormal microtubules. The phosphatase implicated in regulation of tau dephosphorylation, calcineurin, has been shown to be decreased in AD patients [6, 7]. Accumulation of Aβ and tau has also been linked to deficiency of cholinergic receptors, which are key mediators of normal electrical transmission in networks associated with attention, learning, and memory. Aβ exposure also inhibits mitochondrial enzyme activity. Resulting mitochondrial dysfunction leads to the release of free radicals which cause oxidative stress and subsequent neuronal dysfunction [8]. Synaptic dysfunction is also implicated in the pathogenesis of AD [5, 9]. Hippocampal synapses decline in early disease and are disproportionately lost in more advanced disease compared to neurons. Interestingly, this loss correlates better with cognitive impairment than plaques and tangles [10].

Currently, no formalized definition of POCD exists and the mechanism(s) leading to the development of POCD are unclear. It is not possible to classify a patient with POCD using the International Statistical Classification of Disease (ICD-9) code, nor is there standard diagnostic criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Some have questioned the clinical relevance of the term [11], whereas others have referred to dementia diagnosed in the postoperative or postillness situation as postoperative incident dementia [11, 12] and/or postillness cognitive decline [13]. In the absence of specific criteria, POCD is typically defined as a significant and persistent change in mental status as assessed by poorer than expected performance on postoperative neurocognitive testing [14]. The definition of "significant" varies among studies as do the testing modalities. Many of the early studies on POCD focused on cardiac surgery, leading some to conclude that patients presented with memory, attention, concentration, and learning deficits postoperatively [15] and that these deficits were attributable to microembolic events or the abnormal perfusion caused by peristalsis of the cardiopulmonary bypass machine. More recently, however, reports emerged that patients with coronary artery bypass surgeries performed off cardiopulmonary bypass also present with POCD. Age over 70 years old, previous stroke, and major surgery were found to be recurring risk factors for the development of "early" POCD 7 to 21 days after noncardiac surgery [14, 16]. Importantly, patients who exhibit lower neurocognitive function while hospitalized and at 3-month follow-up have a greater mortality risk at 1 year, perhaps, identifying an at-risk population [17].

In contrast to studies that focus on the early postoperative period, most studies do not find a significant difference in the incidence of POCD 1 to 6 months after surgery as compared to control groups [14, 18]. There are less data from studies focusing on cognitive trajectories at greater than 6 months from surgery, but the International Study of Post-Operative Cognitive Dysfunction (ISPOCD) group determined the incidence of cognitive dysfunction in elderly patients after successful noncardiac surgery to be approximately 10% at 1 to 2 years, which is not significantly different from an age-matched nonhospitalized control group [19]. The value of studies which examine cognitive outcomes over a longer time course is that they incorporate the full benefits of the subset of postsurgical elderly patients whose medical conditions were drastically improved with surgery. It might be tempting to regard POCD as a temporary condition that is gradually reversible but we interpret this evidence to demonstrate that older people with medical problems may develop cognitive decline for a great number of reasons and that surgery (with anesthesia) may improve, worsen, or have no major effects on cognition when tested between 6 months and 2 years from their medical treatment.

Preclinical and Clinical Evidence of a Link Between Anesthesia and AD

Preclinical research provides credible evidence that general anesthetic agents may precipitate or exacerbate neurocognitive disorders including AD [20]. In particular, effects of inhaled anesthetics share two major pathologic abnormalities with AD. They increase production and aggregation of Aβ peptides and induce hyperphosphorylation and accumulation of tau [21, 22]. In animal studies, anesthesia exposure leads to phosphorylation of tau at sites specifically affected in AD. In addition to protein abnormalities, inhaled anesthetics also share synaptic failure, mitochondrial dysfunction, and cellular apoptosis as mechanisms of pathogenesis with AD [22].

In mouse models, repetitive exposure to isoflurane in mice with neuropathology of AD increases Aβ peptide aggregates, mortality, and clinically apparent behavioral changes [22]. A nuclear magnetic resonance study confirmed that isoflurane and desflurane promote Aβ peptide oligomerization, which plays an important role in AD pathophysiology, by inducing changes at critical amino acid residues [23]. Aβ peptide aggregation has also been observed in human neuroglioma cells after exposure to isoflurane [24]. Finally, isoflurane has also been found to induce neuroapoptosis via a positive feedback loop that involves the accumulation of Aβ peptide.

Cellular toxicity due to anesthetic agents is not restricted to the nervous system. In another study, sevoflurane and isoflurane induced dose-dependent apoptosis in human T lymphocytes through increased

mitochondrial membrane permeability and caspase-3 activation [25]. It is possible that impairment of immune function contributes to both the progression of AD and the development of POCD [26–30].

Although the adult brain's capacity to regenerate is greatly reduced compared to the developing brain, one parahippocampal region closely associated with memory processing, the dentate gyrus, is capable of new neuron and synapse formation in fully mature rodents [31] and adult humans [32]. Because of this, we may still gain insight from anesthetic-induced neurotoxicity of the developing brain toward better treatment of the adult human brain under anesthesia. Experiments on developing rats exposed to isoflurane, nitrous oxide, and midazolam in relevant concentrations for 6 h triggered widespread apoptosis, hippocampal synaptic dysfunction, and persistent memory and learning deficits [33].

Based on the preclinical data, it is tempting to implicate anesthesia in the induction or exacerbation of AD pathology that causes changes in cognition postoperatively; however, this would be premature. First, in the natural course of AD, pathology can be detected long before clinical symptoms appear (see Figure 1), and the severity of AD pathology does not strictly correlate with the severity of functional impairment [34–36] especially in the setting of cerebrovascular disease [37]. Furthermore, clinical data evaluating the effects of anesthesia on early and late or long-term cognitive impairment are difficult to interpret because of the many variables that affect cognitive status in the perioperative period (e.g. pain, health improvements, and surgical complications). Similarly, the trajectory for cognitive decline in the elderly varies among individuals. There is no single test or biomarker for anesthetic-associated neurodegeneration and, as mentioned above, there is no standard diagnostic criteria for POCD. As a result, many different clinical postoperative scenarios are often referred to as POCD.

Strategies focused on early postoperative cognitive recovery appear to reduce cognitive complications and confusion in elderly patients; shorter-acting and more rapidly eliminated anesthetic drugs are often favored [38–40]. Benzodiazepines have also been found to impair memory and concentration in elderly patients in the postoperative period [41, 42]. Anesthetics such as isoflurane and sevoflurane modulate the central cholinergic system by decreasing acetylcholine release and depressing cholinergic transmission in order to facilitate loss of consciousness, pain, voluntary movements, and memory [43]. Since the central cholinergic system plays an important role in the pathogenesis of AD, it has been suggested that POCD may be an unfortunate unintended consequence of this effect [44, 45]. Recently, a randomized controlled trial showed that anesthetic depth titrated to a bispectral index (BIS) value between 40 and 60 during maintenance of anesthesia reduced anesthetic exposure and decreased risk of POCD at 3 months postoperatively [46]. From this study, the CODA Trial Group determined that 23 patients would be prevented from POCD and 83 patients would be prevented from delirium.

Despite mounting clinical evidence for an association between changes in cognitive baseline and the perioperative period, some retrospective clinical studies have

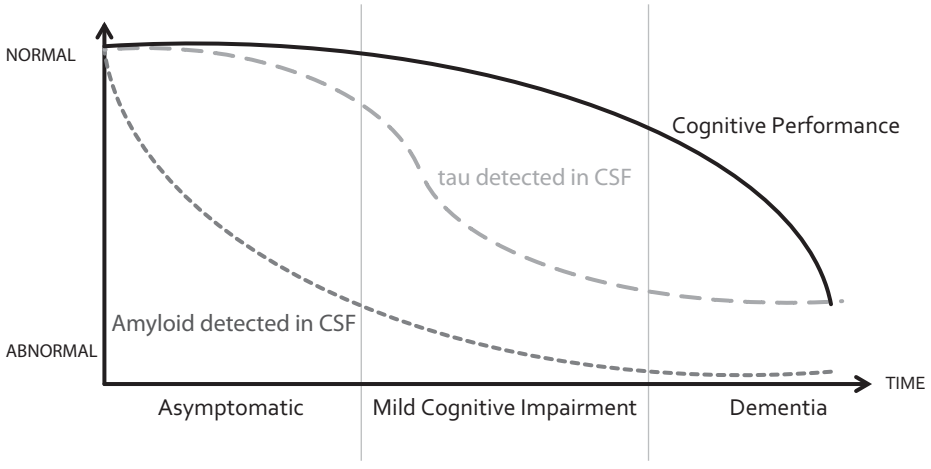

Figure 1. Schematic description of the progression of Alzheimer's disease. Neuropathological hallmarks of disease may appear years before any cognitive manifestation of the disease. Although some anesthesia drugs increase tau and amyloid levels in animal models, it is not appropriate to attribute this as the cause of cognitive impairments associated with the first weeks to months postoperatively given the typical progression of Alzheimer's disease. Schematic modified from data presented in references [34, 62].

failed to detect a difference in persistent cognitive decline specifically attributable to either anesthesia coupled with noncardiac surgery or major illness [47]. A meta-analysis of 15 case–control studies found no significant association between exposure to general anesthesia and risk of developing AD [48]. Furthermore, no association was found between the risk of AD and exposure to anesthesia in the 1 and 5 years prior to AD onset or between the number of surgeries and anesthetic exposures [49]. In summary, the current clinical evidence demonstrates that (1) most patients at risk for AD (the elderly) will not develop persistent cognitive impairment postoperatively, (2) patients develop dementia and AD from a wide array of genetic and environmental factors, and (3) major illness or the perioperative period do not appear to be precipitating factors in hastening or exacerbating the progression of cognitive dysfunction. This evidence should be carefully considered in light of preclinical evidence suggesting potential mechanistic roles of anesthetic drugs in neuropathological consequences. Because of the variability in clinical presentation, it is possible that certain patient subgroups are either more protected from or more susceptible to adverse consequences from anesthesia perhaps due to genetic polymorphisms in proteins involved in the inflammatory cascade or off-target anesthetic drug pathways.

Anesthetic Considerations in the Management of the Patient with AD

Even though anesthesia providers may not be specifically trained to screen for dementia, expert opinion favors performing a cognitive evaluation such as the Mini Mental State Exam (MMSE) before and after exposure to anesthesia [50]. Screening for delirium (i.e. Confusion Assessment Method for the Intensive Care Unit, CAM-ICU [51]) can also aid in early diagnosis, treatment, and potentially prevention. Reducing the incidence of postoperative delirium is critical as it can accelerate the cognitive decline in patients with AD [52]. Evaluating the patient's preoperative functional independence and educating caregivers about postoperative management is important. Caregivers will likely need to be involved in the consent process as well; however, it is important to determine if there is an advanced directive or another healthcare power of attorney. Patients without decision-making capacity should still be included in preoperative discussion to the highest possible extent [53].

Achieving normoglycemia in the intraoperative period is also an important factor for postoperative cognition [50]. Hypoglycemia should always be avoided. Newer evidence indicates that hyperglycemia correlates with occurrence of POCD [54] via two potential mechanisms. First, hyperglycemia during periods of cerebral ischemia can worsen neurologic injury. Second, hyperglycemia enhances the inflammatory response, and this could impact inflammation-mediated POCD. Another potentially important preoperative consideration in AD is investigative questioning about sleep habits and screening for sleep disorders. Sleep disturbances are common in patients with cognitive dysfunction [55] and may provide some insight into abnormal postoperative cognitive trajectories.

Cholinesterase inhibitors are commonly prescribed to patients with AD to increase cholinergic neurotransmitter activity in the CNS, however, the effects are not limited to the CNS. Cholinesterase inhibitors such as donepezil and rivastigmine may increase the duration of action of succinylcholine up to 50 min [50]. Cholinesterase inhibitors also increase parasympathetic activity and may predispose patients to bradycardia. Theoretical concerns with increased cholinergic activity also include risk of ulcers, urinary incontinence, seizures, and obstructive lung disease exacerbations. If an anticholinergic drug needs to be given, glycopyrrolate is recommended because it does not cross the blood-brain barrier [53].

As mentioned above, inhaled anesthetics induce Aβ peptide oligomerization, tau phosphorylation, apoptosis, mitochondrial dysfunction, and synaptic failure in animal models. Although far from being clinically proven, there may be a benefit to avoiding or decreasing inhaled anesthetic exposure if possible in the AD patient. Since tau phosphorylation is increased with hypothermia, maintaining normothermia similarly might be beneficial. Benzodiazepine and longer-acting opioids increase the risk of postoperative delirium, and those should be avoided when possible. Regional anesthesia may improve analgesia while avoiding cognitive effects from opioids. However, a systematic review with meta-analysis showed no significant difference in incidence of POCD or postoperative delirium with general anesthesia as compared to regional anesthesia [56]. One hypothesis for this lack of difference is the concomitant use of sedation with regional anesthesia that may increase the risk and negate the difference. Overall, shorter-acting drugs with faster elimination are recommended to reduce postoperative confusion.

Sophisticated neurocognitive testing (i.e. verbal reasoning and logic testing) immediately postoperatively is of questionable value in patients who may be either in pain or receiving systemic narcotics. However, simple screening exams (e.g. MMSE, CAM, or CAM-ICU) may reliably correspond to acute changes during the recovery period. In patients with difficulty communicating several pain assessments have been standardized for use in nonverbal patients [e.g. Pain Assessment in Advanced Dementia Scale (PAINAD) and Pain

Assessment for the Dementing Elderly (PADE)]; these are reviewed in [57, 58]. Their use postoperatively has not been established but deserves some consideration, especially since some patients could be in unrecognized pain due to a hypoactive, nonverbal delirium after surgery.

Delirium complicates the postoperative course in 15% to 53% of patients aged 65 years or older and can lead to loss of independence, increased risk of morbidity and mortality, and increased healthcare costs [59]. In addition, delirium can accelerate the decline in cognitive function in patients with AD [52]. Although many risk factors for postoperative delirium cannot be ameliorated, there are some that can be modified. Cholinergic deficiency plays a role in delirium and administration of anticholinergic drugs can lead to delirium. Physostigmine, a reversible cholinesterase inhibitor, reverses delirium caused by anticholinergic drugs and has some benefit in treating delirium not caused by anticholinergic drugs [60]. Another pharmacologic treatment strategy is the prophylactic use of neuroleptics like haloperidol, risperidone, and olanzapine. In addition to efficacy with postoperative nausea and vomiting, antipsychotic medications have been shown to reduce the risk of postoperative delirium in elderly patients [61]. Although patients with dementia are at increased risk for delirium, the use of perioperative antipsychotics in patients with dementia has not been specifically examined.

Conclusions

The preclinical and clinical evidence that link adverse effects of anesthesia to either a deterioration of cognitive function or an exacerbation of neurodegeneration in susceptible individuals merits concern. This review presents both preclinical and clinical data for consideration that highlight the potential interactions between AD and POCD. It is also critical to consider the potential consequences of determining if such a link exists. In many circumstances, it is not possible to do surgery without anesthesia on patients. Similarly, it is still unclear if postoperative changes are due to the effects of anesthesia, surgery, inflammation, or the expected cognitive trajectory of an individual with predisposing factors for cognitive deterioration. Perhaps the most difficult consideration in determining the role of anesthesia in POCD or AD is the difficulty in identifying the appropriate control groups. Excepting the most minor elective or cosmetic procedures, most elderly persons undergo surgery for a particular purpose and it is difficult to find comparable patients in a similar state of health that are choosing not to have surgery. Those awaiting definitive clinical evidence for causation cannot be satisfied as it is not possible to randomize patients into groups that will or will not develop AD or surgical diagnoses. After every procedure, an important question is raised: "Where would the patient's cognitive (and health) status be if they were to not have had surgery and anesthesia?"

Declaration of Interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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