

## Alzheimer disease and anesthesia

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**Abstract:** Alzheimer disease (AD) is one of the most common neurodegenerative diseases and the most prevalent form of dementia. Some factors in the development of AD, age being the best-known one, have been suggested; however, no causes have been found yet. The pathophysiology of the disease is highly complex, current therapies are palliative, and a cure is still lacking. Adverse effects of anesthetics in the elderly have been reported since the 1950s; however, awareness of this old problem has recently gained importance again. Whether exposure to surgery and general anesthesia (GA) is associated with the development of AD has been questioned. As the population is aging, many elderly patients will need to be anesthetized, and maybe some were already anesthetized before they were diagnosed. Exposure to anesthetics has been demonstrated to promote pathogenesis of AD in both in vitro and in vivo studies. However, to date, there have not been any clinical trials to address a link between exposure to GA and the development of AD in humans. Therefore, before making any conclusions we need further studies, but we should be aware of the potential risks and take cautions with vulnerable elderly patients.

**Key words:** Alzheimer disease, anesthesia, postoperative cognitive dysfunction

### 1. What is Alzheimer disease? Definition, facts, cause or risk factors, and pathophysiology

The Alzheimer's Association defines Alzheimer disease (AD) as an irreversible and progressive fatal brain disease that causes problems with memory, thinking, and behavior. AD is the most common cause of dementia, not a normal part of aging with still unknown cause and cure. Because of increased life expectancy, during the next 25 years the number of people with AD in the United States is expected to increase by about 40% more than the current prevalence, just as the costs associated with AD will increase (1).

The disease develops as a result of multiple factors such as advanced age, female sex, lower educational status, family history, and specific genetic mutations. A very small percentage of people with AD (less than 5%) have the familial form. AD has still unknown genetic and environmental risk factors contributing to its development. The link between exposure to environmental chemical agents and AD has been suspected, providing a potential relation for the possible role of general anesthesia (GA) in AD pathogenesis. With a substantial population being affected by this disease, it is likely that not only neurologists or psychiatrists but also all physicians including anesthesiologists in the coming years will encounter many patients with AD.

The pathogenesis of this disease is complex, involving molecular, cellular, and physiological pathologies. The pathological changes are similar to normal aging qualitatively, but different quantitatively. Two major protein abnormalities are mainly responsible in the pathogenesis of the disease:  $\beta$ -amyloid peptides ( $A\beta$  peptides) and tau.  $A\beta$  peptides are normal products of metabolism, but an imbalance between production and clearance occurs in AD and excess  $A\beta$  peptides aggregate as extracellular plaques. Tau protein is normally responsible for stabilization of microtubules and transportation of vesicles. In AD, tau protein is hyperphosphorylated, and this form causes abnormal microtubules and forms intracellular neurofibrillary tangles (2). These two main abnormalities contribute to neurotoxic processes including oxidative stress, inflammation, failure of synaptic function, depletion of neurotransmitters, and eventually cell death. Finally, all together, they cause AD. Macroscopic changes include global brain atrophy, ventricular enlargement, and widening of sulci that are more prominent in frontal and temporal lobes; subsequently, there is an overall shrinkage of brain tissue (3).

Diagnosis of AD is still clinical or based on microscopic examination of the brain on autopsy; however, several diagnostic tests have been developed to help confirmation.

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It is well known that cerebrospinal fluid biomarkers are characterized by an increase in total and phosphorylated tau, but a decrease in A $\beta$ . Advanced medical imaging with computed tomography, magnetic resonance imaging, single-photon emission computed tomography, or positron emission tomography are recommended for routine evaluation of AD and these imaging methods help to exclude other cerebral pathologies or subtypes of dementia.

## 2. AD and anesthesia

### 2.1. Postoperative cognitive functions

It has been suggested that an association among anesthesia, surgery, delirium, postoperative cognitive dysfunction (POCD), and dementia exists. Depending on the age of the patient and the type of surgery, delirium is an extremely common and distressing postoperative complication with a prevalence of 10%–15% in elderly patients who receive GA. POCD is also a common complication in the early weeks following surgery and anesthesia. Whether POCD is reversible or not is still unclear, and whether it is associated with the anesthesia or surgery remains controversial. It is particularly common following cardiac and orthopedic procedures. POCD after anesthesia may represent the cognitive decline that occurs in elderly people and is known to precede the dementia of AD.

Bedford first reported postoperative confusion in elderly patients as early as 1955. He reviewed 1193 patients over 50 years old who had received GA and found that 10% of his patients had POCD; he suggested anesthetic agents and hypotension to be probable causes of cognitive dysfunction. He recommended that operations on elderly patients be limited in terms of unnecessary procedures. On that basis, the first International Study of Postoperative Cognitive Dysfunction (ISPOCD) reported the next major study of POCD in 1998 (4). In noncardiac patients of more than 59 years old, the incidence of cognitive dysfunction 1 week after surgery was 22% higher and 3 months after surgery was 7% higher than in age-matched controls. Similar to Bedford's finding, 10% of patients presented with POCD. Increasing age, duration of anesthesia, lower educational status, repetitive operations, postoperative infection, and respiratory complications were reported as risk factors for early POCD and only age remained statistically significant during the 3-month follow-up among the risk factors.

### 2.2. Is GA a risk factor for AD?

For a long time, it was assumed that most anesthetics have neuroprotective effects. In particular, barbiturates, volatile anesthetics, and propofol are known to inhibit ischemic cascades by suppressing excitatory neurotransmitters and potentiating inhibitory ones. However, recently doubt about their neurotoxicity, especially at extreme ages

in neonates and the elderly, has been arising and new evidence has suggested that they may be responsible for a number of sequelae following exposure.

Preclinical evidence from animal models and in vitro studies has suggested the potential relation between GA and AD. Association between exposure to GA and the development of AD has been shown in transgenic mouse models (5), and A $\beta$  peptide-related processes and tauopathy have been observed in animals exposed to GA (6).

There is essentially a lack of evidence to suggest anesthetics-induced neurotoxicity in humans. There have been no randomized controlled clinical trials examining the risk of AD associated with exposure to anesthesia. The only randomized controlled trials were held based on comparison of the effects of general versus regional anesthesia on the risk of POCD (7). Nevertheless, to provide evidence-based observational studies, case-control and cohort studies have gained importance. In a recent report (8), epidemiological evidence for GA as a risk factor for AD was reviewed. Methodologically, the authors preferred to exclude cognitive outcomes rather than dementia, such as delirium or POCD, and no evidence was found that suggested any link between exposure to GA and development of clinically diagnosed dementia. The same group also published a metaanalysis of 15 case-controlled studies that met their inclusion criteria (9). None of the studies demonstrated a significant increased risk of AD associated with GA individually; they also failed to demonstrate any evidence of increased risk of AD following previous exposure to GA compared to no history of GA exposure in the metaanalysis. In a recent population-based case-control study carried out at the Mayo Clinic, it was concluded that receiving GA for procedures after the age of 45 years old was not a risk factor for incident dementia (10).

However, some reviews suggested that exposure to anesthetics would promote the risk of AD. In patients 80 years old or older, AD was found to be associated with exposure to GA. Chen et al. (11) also showed a significantly increased risk in development of dementia 3–7 years after anesthesia and surgery.

There has been no prospective cohort study on this topic. Similar to case-control studies, the results of the limited number of retrospective cohort studies are also unsettling. Lee et al. (12) compared the risk of developing AD 5–6 years after coronary artery bypass graft (CABG) surgery under inhalational anesthesia versus the risk of developing AD within 5–6 years of percutaneous transluminal coronary angioplasty (PTCA). In the CABG patients, AD developed more often than in PTCA patients. Vanderweyde et al. (13) evaluated the risk of AD following exposure to GA compared to local anesthesia in two surgical cohort studies on prostate and hernia surgeries.

In that analysis, in contrast to previous findings, exposure to GA was associated with a reduced risk of AD when compared to local anesthesia.

Preclinical studies suggest that anesthetics may affect cognition by mimicking the molecular mechanism in the pathogenesis of AD (Figure).

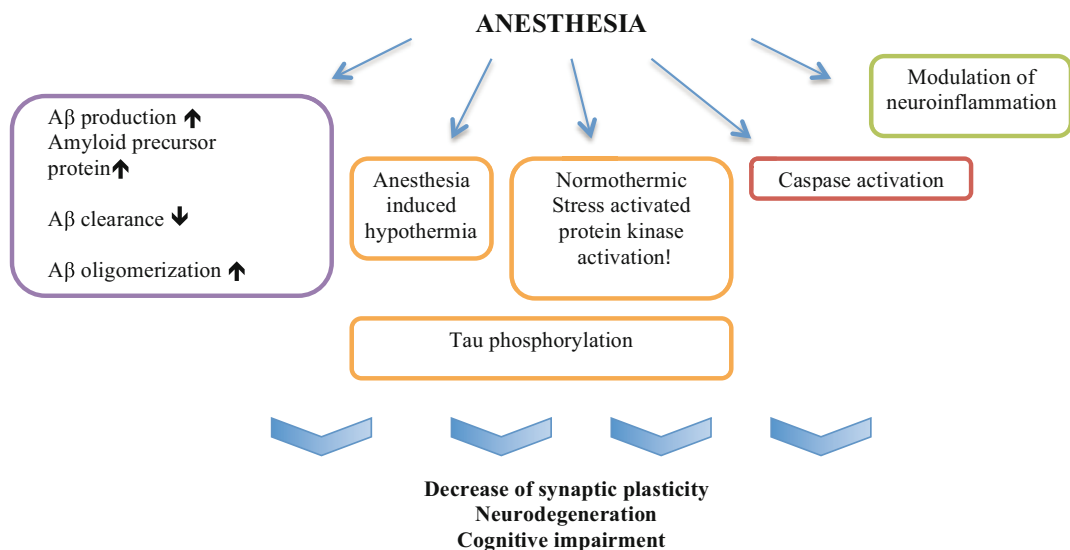
In particular, effects of inhaled anesthetics share two major pathologic abnormalities with AD. They increase production and aggregation of A $\beta$  peptides and induce hyperphosphorylation and accumulation of tau. Anesthetics facilitate disinhibition of protein binding and thus help monomers to aggregate. If those monomers are A $\beta$ , this oligomerization results in neurotoxicity. Inhaled anesthetics have also been demonstrated to increase the formation of AD precursors in both in vivo models and in vitro studies (14,15).

In 2004, Eckenhoff et al. (16) initiated neurotoxicity studies and demonstrated that the inhalation anesthetics isoflurane and halothane enhanced A $\beta$  oligomerization in vitro and potentiated A $\beta$ -induced cytotoxicity in rat pheochromocytoma cells. Xie et al. (14) studied the effects of isoflurane on apoptosis and A $\beta$  levels in human neuroglioma cells and reported that treatment with 2% isoflurane for 6 h induced caspase-3 activation, cell death, and accumulation of extracellular levels of A $\beta$  in the cells. Despite these findings suggesting that isoflurane is neurotoxic, there have been many reports that suggest that isoflurane may protect against neurotoxicity. Isoflurane's protection effects have been shown to be dual, both dose- and time-dependent (17).

When compared with isoflurane, halothane led to more amyloid deposition in transgenic mice than isoflurane. Sevoflurane was also associated with increases in A $\beta$  in mouse models (18). Desflurane, a newer inhalation anesthetic, different from isoflurane and sevoflurane, was shown to have no effect on caspase-3 activation, APP processing, and A $\beta$  accumulation in human neuroglioma cells and does not induce learning and memory impairments in mice (19). Similar to desflurane, Zhen et al. (20) showed that nitrous oxide did not cause apoptosis or A $\beta$  accumulation in cells and neurons. In summary, these findings suggest that nitrous oxide and desflurane have preferable features in regards to their effect on A $\beta$  protein as compared to the other commonly used inhalation anesthetics, isoflurane and sevoflurane (6).

Palotas et al. first investigated the effect of propofol on A $\beta$  protein (21). They studied the effects of propofol on the precursor protein of A $\beta$  (APP) in rats and found that propofol does not affect APP. Moreover, propofol was found to inhibit isoflurane-induced A $\beta_{42}$  oligomerization (22). These data may suggest that propofol does not promote A $\beta$  pathology.

Molecular size of the anesthetic seems to be the significant contributing factor in inducing A $\beta$  oligomerization. Magnetic resonance imaging studies suggest that smaller-sized agents like volatile anesthetics can promote A $\beta$  oligomerization whereas larger-sized intravenous agents cannot interact with A $\beta$  protein and do not promote A $\beta$  oligomerization (halothane > isoflurane > sevoflurane > propofol > thiopental > diazepam) (23).



**Figure.** Schema of how anesthesia causes AD.

Both preclinical and early clinical studies suggest that anesthetics can accelerate tau pathology by inducing massive and rapid hyperphosphorylation of tau. This effect may be independent of the anesthetic used, but the presence of hypothermia during anesthesia, a common clinical occurrence, appears to exacerbate the degree of phosphorylation. Furthermore, reestablishing normothermia during anesthesia was shown to restore tau phosphorylation to normal levels (15).

However, anesthesia-induced hypothermia appears to not be the only reason for the development of tauopathy, since tau phosphorylation has been reported in normothermic conditions. This second mechanism represents a direct way, independent of hypothermia, and involves stress-activated protein kinase activation. Whittington et al. (24) suggested that hypothermia, which is common in the elderly, might enhance AD pathology. The same group investigated the effect of propofol on tau phosphorylation under normothermic conditions and found that hyperphosphorylation still occurred in the absence of hypothermia. Subsequently, they examined the impact of dexmedetomidine and found similar tau hyperphosphorylation under normothermic conditions. With a further study, Le Freche et al. (25) observed that acute exposure to the inhalational anesthetic sevoflurane resulted in significant dose-dependent tau hyperphosphorylation in the hippocampus of nontransgenic mice under normothermic conditions and suggested that this is not specific even for intravenous anesthetics. Nevertheless, the impact of anesthesia with hypothermia or not on tau pathology should not be underestimated as the number of patients having surgery increases steadily.

### 2.3. Surgery, neuroinflammation, and AD

Relations between surgery, anesthesia, AD, and neuroinflammation have been studied. Much of the evidence has derived from animal studies; human studies on this topic are rare. It appears that neuroinflammation plays an important part in the neuropathogenesis of neurodegenerative disorders like AD. Both surgery and anesthesia produce neuroinflammation to some degree separately. Surgery initially causes a peripheral inflammation response and as this inflammation is transferred to the central nervous system (CNS) depending on neurohumoral factors and encountering the blood/brain barrier, a systemic inflammatory response is produced. The mechanism of the way in which surgery impairs cognition is not yet clear, but possibly stress-induced hormonal responses, inflammatory cascades, and circulatory, respiratory, and temperature instability due to surgery are involved. The role of surgery-induced inflammation in POCD is enhanced by age (26).

Anesthesia has both antiinflammatory and proinflammatory effects. However, anesthetics are

supposed to have neuroinflammatory effects depending on the drug and dose administered. Intravenous agents such as propofol and ketamine do not cause neuroinflammation, whereas with volatile anesthetics, and especially with isoflurane, neuroinflammation was noted.

Nevertheless, anesthesia and surgery have been rarely administered separately to allocate their impairment on postoperative cognition. It is difficult to say that surgery or anesthesia alone is the cause of postoperative decline, and it is certain that surgery and anesthesia together potentiate each other's effect and lead to a steeper decline in cognitive functions. In vulnerable patients, such as the elderly or possible AD patients, it appears that anesthesia and surgery would promote neuroinflammation and AD pathogenesis.

### 2.4. Do anesthetic techniques differ in the risk of AD?

Most reviews indicated that there was limited evidence to suggest any difference between GA and regional anesthesia for the risk of POCD (27–29).

Absence of further evidence to suggest any difference between GA and regional anesthesia on the incidence of POCD can be explained by the use of intravenous sedation with regional anesthesia that may increase the risk and negate the difference.

Nevertheless, Wu et al. (27) failed to show a difference between different anesthesia techniques on the development of POCD in their systematic review. In a clinical update (29), GA was compared with regional anesthesia for their influences on delirium or POCD. A total of 18 randomized controlled trials were identified, 2 evaluating delirium, 10 evaluating POCD, and 6 evaluating both; no significant difference was found.

On the contrary, a review of anesthesia for hip fracture surgery found a reduction in acute postoperative confusion with regional anesthesia compared to GA (30). However, the authors concluded that the evidence from the trials was not sufficient enough to rule out any clinically important conclusions. Mason et al. (28) in their systematic review with metaanalysis compared the influence of general, regional, or combination anesthesia on the development of POCD and postoperative delirium (POD). They found an increase in the incidence of POCD but not POD with GA. Vanderweyde et al. (13) compared effects of GA and local anesthesia on the risk of developing AD in patients undergoing either prostate or hernia surgery. Exposure to GA did not increase the risk of AD, and interestingly it was associated with a reduced risk of AD when compared to local anesthesia.

However, randomized controlled trials comparing different anesthetic techniques found little or no difference in long-term follow-up for persistent POCD following exposure to GA when compared to regional anesthesia (31).

If GA is mandatory in the case of a possible regional anesthesia contraindication or due to necessity of surgical procedure, then a decision for maintaining anesthesia with intravenous or inhalation anesthetics should be made. Inhalational anesthesia has been associated with higher risk of cognitive impairment in both in vivo and in vitro studies. However, currently there are not enough clinical studies to prove that inhalational anesthesia causes dementia or AD in humans.

The inhalation anesthetic isoflurane has been shown to induce caspase activation and increase A $\beta$  accumulation, which are associated with the key pathological pathways in AD. In contrast, propofol has been reported to have neuroprotective effects. Zhang et al. (22) compared the effects of isoflurane and propofol individually and in combination on A $\beta$  oligomerization in vitro and in vivo. Isoflurane alone induced A $\beta$ 42 oligomerization, whereas propofol inhibited the isoflurane-mediated oligomerization of A $\beta$ 42. Propofol would be a better choice of anesthetic especially in vulnerable elderly and AD patients.

### 3. Anesthetic considerations in patients with or at risk of AD

Anesthetic management in elderly patients requires appropriate preoperative evaluation, maintenance of hemodynamic stability, and awareness of impairment of circulatory and other systems by aging. Proper preoperative consultation and information about such potentials can be helpful to reduce the patient's and the family members' anxiety.

Preoperative clinical assessment requires not only physical status evaluation but also evaluation of cognitive reserve. Performing a preoperative careful cognitive evaluation using the Mini Mental State Exam (MMSE), for example, before and after exposure to anesthesia may be mandatory for all elderly patients undergoing general anesthesia.

Biomarkers of the disease may be present many years before clinical symptoms become apparent. CSF analysis of tau and A $\beta$  proteins is an important part of AD screening. Xie et al. (32) studied the association of the AD biomarker with changes in cognitive functions after elective surgery and, consistent with previous findings, they found that the presence of the AD biomarker preoperatively, specifically the A $\beta$ /tau ratio, may help to predict patients at higher risk for cognitive changes after surgery. Silbert et al. (33) suggested that anesthesiologists can play a key role in CSF sampling, as they are skilled in lumbar puncture for spinal anesthesia during routine anesthesia practice. However, some ethical and moral issues, including informed consent for CSF sampling and analysis, should be considered. Even the biomarkers can show the presence of AD before the

onset of symptoms, at present a cure is not available, and some patients would prefer not to learn the results. Similar ethical concerns are valid for genetic identification.

Particular precautions taken by the anesthesia and surgical teams can prevent intra- and postoperative complications and thereby reduce the risk of postoperative cognitive decline (Table). Decisions can be made regarding the extent of the procedure considering risks versus benefit, or even whether an elective procedure should be canceled. Surgeons must use meticulous surgical techniques, minimally invasive if possible.

Age-related systemic impairments, malnutrition, poor hygiene, incontinence, and chronic diseases may be present in patients with or at risk of AD at the time of surgery. Anesthesiologists must carefully review the patient's medical history, evaluate systemic functions, and check the prescribed and unprescribed medications considering possible drug interactions. Attention should be paid to preoperative sedation, especially with benzodiazepines, because it may worsen postoperative mental confusion. Dressler et al. (34) demonstrated memory impairment in patients premedicated with midazolam on the first postoperative day.

Although far from being clinically proven, there may be a benefit to avoiding or decreasing inhaled anesthetic exposure if possible in the AD patient.

It is essential to provide a tight intraoperative homeostasis and keep the patient's fluid, electrolyte, oxygen, and glycemic balances to reduce cognitive impairment. Studies show that achieving normoglycemia during the intraoperative period improves postoperative cognition. Both hypoglycemia and hyperglycemia should be avoided.

Anesthesia-induced hypothermia is known to cause tau hyperphosphorylation and could be reversed if normothermia is sustained (35). Thus, monitoring temperature and maintaining normothermia are mandatory.

Fast-track anesthesia techniques seem to reduce postoperative cognitive impairment and enable the patient to cooperate earlier in the postoperative period. For this reason, shorter-acting and rapidly eliminated anesthetic drugs would improve early postoperative cognitive recovery and reduce cognitive complications and confusion in elderly patients. However, benzodiazepines have been found to impair memory in the postoperative period and sedation with benzodiazepines is not favored. As delirium can accelerate postoperative cognitive decline, it is important to decrease risk factors for POD. Cholinergic deficiency plays a role in delirium and administration of anticholinergic drugs can lead to delirium. To reduce the risk of POD in elderly patients, physostigmine, reversible cholinesterase inhibitors, and prophylactic use of

**Table.** Anesthetic management of patients with AD

Preoperative evaluation	Preoperative assessment
	Comorbid diseases
	Prescribed medication
	Family history
	Previous surgeries
	Habits: Alcohol, cigarettes, eating, sleeping
	Informed consent
	Early diagnosis
	CSF sampling?
	Ethical concerns
Cognitive evaluation - MMSE	
Perioperative management	Monitoring
	Glycemic balance, temperature, depth of anesthesia
	Anesthetic technique
	Cautious use of sedatives - avoid benzodiazepines
	Decrease inhaled anesthetic exposure
	Regional anesthesia?
	TIVA?
	Shorter-acting and more rapidly eliminated anesthetics
	Reduce risk of POD
	Avoid atropine
	Use prophylactic neuroleptics
	Prescribed cholinesterase inhibitors
	Aware of increased cholinergic activity
Avoid succinylcholine	
Prefer short acting NMBA	
Spontaneous recovery of NM blockade	
Sugammadex?	
Postoperative interventions	Early extubation
	Effective analgesia and if necessary sedation
	Avoid benzodiazepines
	Education and support

neuroleptics like haloperidol are advantageous treatment strategies. Zhang et al. (36) in their metaanalysis suggested sedation with dexmedetomidine and antipsychotics for prevention of POD.

Commonly, patients with AD are prescribed cholinesterase inhibitors to increase cholinergic neurotransmitter activity in the CNS; however, the side effects are not limited to the CNS. Cholinesterase inhibitors may increase the duration of action of succinylcholine and predispose patients to bradycardia. Theoretical concerns with increased cholinergic activity also include risk of ulcers, urinary incontinence, seizures, and obstructive lung disease exacerbations.

Reducing the volatile agent exposure by monitoring anesthetic depth has also been questioned; however, study findings are inconsistent and an assessment of this issue is not yet possible. A recent randomized controlled trial (37) showed that keeping the depth level of anesthesia with BIS

between 40 and 60 was associated with a lower incidence of POCD and delirium at 3 months postoperatively.

#### 4. Conclusion

It is very difficult to draw any conclusions about the anesthetic agents to be used or avoided in patients with AD. Further comprehensive research is required to review the anesthesia protocols so as to limit the impact of anesthesia on patients with or at risk of AD. At the present time, there is no evidence to support an association between exposure to GA and increased risk of AD based on available clinical data. The existing literature is insufficient due to a lack of human studies. However, we cannot ignore evidence from both in vivo and in vitro studies indicating potential risks. Elderly patients and their families should be warned about the possibility of postoperative cognitive decline and efforts should be made to optimize the perioperative care of older patients. Using human biomarkers and neuroimaging

modalities might gain importance in the future or lead new discussions on ethical issues. The decision of which anesthetics to choose should be made on the basis of the surgical procedure and other factors related to the patient.

There is a strong need for adequately powered, long-term, prospective cohort studies or randomized controlled

trials or retrospective studies for further understanding the association between anesthesia and the risk of AD in humans after surgery. The expanding life expectancy indicates consideration of this issue since we might be the ones who relying on these improvements one day.

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