# Alzheimer's disease, anesthesia and the cholinergic system

Alzheimer's disease (AD) is a degenerative brain syndrome characterized by a progressive decline in memory, thinking, comprehension, calculation, language, learning capacity and judgment, sufficient to impair personal activities of daily living. This editorial has been penned to update the readers on the advances in the understanding of AD, its relation to anesthesia, interactions with anesthetic agents and the perioperative concerns in patients with AD. AD is characterized by a compromised neuronal transmission and thus the choice of anesthetic drugs may have different effects on patient outcome.

AD is a form of dementia, resulting from the degeneration of basal forebrain cholinergic neurons innervating the cortex amygdale and hippocampus.[1] Cognitive impairment, personality change, psychotic symptoms, incontinence, gait and motor disturbance, seizures and myoclonus can occur.[2] There is a significant impairment in social and occupational function. AD is a devastating disease. Brains of AD patients have gross diffuse atrophy of the cerebral cortex with the secondary enlargement of the ventricular system. It is a leading cause of death, increasing the mortality of those affected by up to 40%.[3] A MetLife Foundation survey revealed that amongst Americans the fear of getting AD is greater than the fear of cancer.[4]

AD is the main cause of dementia today in people over 65 years of age. It is a common worldwide public health problem and the World Health Organization (WHO) estimates that over 18 million people in the world suffer from AD. This figure is projected to nearly double to 34 million by the year 2025.[5] The prevalence of this disease is increasing and much of the increase is in the developing countries, with a shift of their population spectrum to the geriatric end. Increasing longevity will inevitably lead to an increase in the number of patients with AD.[6] With a substantial population being affected by this disease, it is likely that anesthetists in the coming years will encounter many patients with AD.[7] In this issue, we have three reports describing different aspects of delivery of anesthesia in patients suffering from degenerative central nervous system diseases. The simultaneous submission of three case reports of patients suffering from these diseases highlights the fact that more such patients are being administered anesthesia.


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Degenerative diseases of the brain are associated with deficits in the cholinergic system. The cholinergic system is an important modulator in the brain and is vital for conscious awareness. Acetyl Choline (ACh) regulates high cognitive functions such as memory, learning, dendrite arborization, neuronal development and differentiation.[2] Cholinergic receptors are classified into nicotinic (nAChRs) and muscarinic (mAChRs) receptors. nAChRs are expressed in both the peripheral and central nervous system. nAChRs are located in the neuromuscular junction, on ganglionic cells and on non-neuronal cells.[2] Loss of cholinergic neurons is thought to be responsible for the learning and memory deficits. The pathological changes consist of progressive accumulation of insoluble fibrous material in extracellular and intraneuronal locations in the central nervous system. Amyloid protein plaques occur 10 to 20 years before symptoms develop. Extracellular deposits are formed of A4 amyloid, whereas intraneuronal components represent the neurofibrillary changes composed of abnormally phosphorylated tau protein.[7] Amyloid deposits and neurofibrillary changes occur in both hemispheres but the distribution may not be symmetrical.[8]

The sensitivity of cholinergic receptors to anesthetic drugs plays an important role in determining various stages of narcosis.[9] During general anesthesia, decrease in ACh release and depression of cholinergic transmission facilitate effects of anesthetic agents, such as loss of consciousness, pain, voluntary movements and memory.[10] Several anesthetic agents and drugs administered during anesthesia interact with the central cholinergic system. Most of the anesthetic agents interact with both nAChRs and mAChRs. nAChRs are thought to be involved in the mechanism of action of inhalational anesthetic agents.[11] The main effect of anesthetic agents on nAChRs is inhibitory.[12] Binding of anesthetic agents to both these receptors modulates cholinergic transmission and has profound effects on brain function.

The inhalational anesthetics bind both the cholinergic receptors in a dose-related manner.[13] Barbiturates are strong competitive antagonists of mAChRs but propofol acts on the nAChRs and mAChRs only at higher than therapeutic

plasma concentrations.[13] Opioids, morphine and fentanyl may block both the receptors but remifentanil does not interfere with ACh release.[14] Atracurium and its metabolite laudanosine activate a4b2 subtype nAChRs and may have a neuroprotective role.[15]

There is no definitive treatment for AD. No therapy is also available that can halt the progression of AD but there are a few therapies to delay its progression.[16] No currently available drug consistently confers significant clinical benefit. Care is mainly limited to control of behavioral and neurologic problems in conjunction with support and education of family and caregivers. Depression is common in early stages and it may respond to antidepressant agents. Mild sedation may help insomnia. Agitation can be controlled by low-dose haloperidol.

Centrally-acting cholinesterase inhibitors (ChIs) are the mainstay in the treatment of AD. ChIs increase the cerebral levels of ACh. Tacrine is associated with improved patient function and a decreased rate of decline in cognitive test scores. However, Tacrine has no benefit in late AD and is potentially hepatotoxic. Donepezil, a reversible, noncompetitive, piperidine-type ChI, has the advantage of fewer side-effects and single daily dosage and is more commonly used today. Rivastigmine blocks the breakdown of ACh and has been shown to be effective in improving measurements of thinking, daily living activities, and behavior.[17] ChIs may prolong the half life of suxamethonium, to about 50 min, by inhibiting pseudocholinesterase. ChIs also antagonize the effects of atracurium by blocking ACh hydrolysis.[18] Chronic use of ChIs down-regulates postsynaptic ACh receptors and could affect response to nondepolarizing neuromuscular blockers.[19]

Adverse effects of ChIs may limit the total dose prescribed and so patients may not be in receipt of adequate dosage for control of the symptoms. Peripheral cholinergic adverse effects of ChIs include nausea, vomiting, diarrhea, dizziness, syncope and even seizure and they may cause discontinuation of therapy.[20,21] Seizures can also be due to the disease process itself. Detrusor hyperactivity may result in urinary incontinence. ChIs may aggravate asthma and obstructive lung disease by increasing secretions. Vagal tone stimulation can cause cardiac dysrrhythmia.[22] In patients with sinus node disease or with other supraventricular conduction anomalies' effects excessive cholinergic state may be clinically evident. Bradyrrhythmias due to sinus node dysfunction, needing pacemaker implantation, have been reported after donepezil therapy.[23] Pacemaker implantation permits continuation of ChI therapy and increase in dosage, if required.[24]

Other drugs being evaluated for the treatment of AD include estrogen (in post-menopausal women); monoamine oxidase B inhibitor selegiline and Vitamin E (antioxidants); nonsteroidal anti-inflammatory agents and selective COX-2 inhibitors (anti-inflammatory); herbal extract, ginkgo biloba (cerebral vasodilatation and protection of vascular endothelium from toxic effects of amyloid beta peptide); neurotrophic factors that can cross the blood-brain barrier; and a vaccine against the disease.[7]

Preoperative assessment may be difficult as the patient is disoriented, uncooperative, confused and at times violent. Complete history may be difficult to elicit and clinical examination may remain incomplete. AD patients may have age-related systemic impairments, nutritional deprivation, poor hygiene, incontinence, chronic disease, history of subdural hematomas, hip fractures, and may have effects of smoking/alcohol. The anesthesiologist must carefully review the medications that the patient is receiving, including herbal preparations.[7] Drug interactions with anesthetic agents should be considered, especially with antidepressant drugs and appropriate plans made. Consent may need to be given by the caregiver, who too may be under extreme mental and physical stress. Perioperative sedation should be carefully prescribed because it may aggravate mental confusion. Benzodiazepines deteriorate symptoms, worsening acute confusion and delirium, and increase sedation.[24]

AD patients are often disoriented and uncooperative, making regional anesthetics potentially challenging. Fragile skin, weak bones, bradykinesia and stiff joints with limited range of motion demand careful and gentle intraoperative positioning and adequate padding. Segmental neuraxial blocks can be achieved with smaller doses of local anesthetic due to reduced vascular uptake and shortened vertebral column length. Prolonged immobilization increases the incidence of deep venous thrombosis and pulmonary embolism. Use of sedatives as adjuvant to facilitate the conduct of a regional anesthetic may make the patient more uncooperative due to aggravation of confusion.

There are no specific indications to the use of intravenous anesthetics or inhaled anesthetics; however, pharmacokinetic alterations in the elderly and speed of recovery to the preoperative level of mental function should be considered, especially if the patient is to be cared for in an ambulatory setting. Glycopyrrolate, which does not cross the blood-brain barrier, would be preferable to scopolamine or atropine as an anti-sailagogue agent.[25] There is a decreased response of β receptors to agonists and antagonists' drugs. Etomidate may be employed on induction because of its cardiac stability. Age-related reduction in minimum alveolar concentrations of inhalational anesthetics and minimum intravenous concentration of intravenous agents need to kept in mind.

It has been suggested that postoperative cognitive dysfunction (POCD) and delirium are possible consequences of anesthetic agents interacting with AChRs to produce inhibition of central cholinergic transmission, already impaired by age-related changes.[14] POCD may appear within five days after surgery and monitoring for its possible advent should be done during this period.[24] Hypothermia has been implicated to cause tauhyperphosphorylation in animals and it is postulated that peripostoperative hypothermia may play a major role in the development of POCD or AD.[24]

Combination of general and regional anesthesia is preferable, when feasible, to reduce the intra and postoperative opioid load. Objective pain evaluation tools, based on observation of the patient at rest/during movement/care activities, should be used as patient may not be able to comprehend. Postoperative analgesia/sedation should be based on the principles of local/regional analgesia or short-term analgesia/sedation. Prolonged mechanical ventilation is a risk factor for the development of POCD, because deeper sedation needs to be administered.[26] It has been suggested that patients with AD will benefit from early progressive reduction of the analgesia/sedation regime and early extubation.[24] The amount of blood components' transfusions appear to be correlated to the development of POCD.[27] Strategies for blood conservation must be adopted. In case POCD occurs it should be treated with the use of neuroleptics and olanzapine.

Exposure to general anesthesia has been proposed as a potential risk factor for AD. Elderly subjects exposed to anesthesia have been reported to experience long-term cognitive impairment with clinical features of dementia, suggesting that surgery and anesthesia could increase the risk of AD or accelerate its progression.[28] California Alzheimer Disease Diagnostic and Treatment Center Program data indicates that vascular dementia subjects were more likely to have a history of general anesthesia.[29] The incidence of POCD is increased after cardiac surgery and reflects severe neuronal injury mimicking pathogenetic events seen in AD patients. Several research groups are now investigating the neurotoxic effect of anesthetic drugs and combinations of drugs.[30] Genetic predisposition to develop AD has been suggested and it has been proposed that before surgery requiring anesthesia, it may be ideal to know the genetic background of the patients so that the drugs used and the pattern of anesthesia is personalized accordingly.[31]

Bohnen *et al.*, evaluated prior exposure to general anesthesia as a potential risk factor for AD but found no association of AD with general anesthesia in patients more than 50 years of age. However, they reported an inverse relationship between age of onset and cumulative exposure to general and spinal anesthesia before the age of 50, indicating a possible relationship between dementia and exposure at an earlier age.[32] Gasparini *et al.*, in a retrospective study, however, found no associations between the risk of AD and the exposure to anesthesia, one to five years preceding disease onset, and also between the risk of AD and the number of surgical operations.[33]

To conclude, evidence from animal models suggests that inhaled anesthetic exposure increases pathology normally associated with AD. Human studies on anesthesia and AD are however inconclusive because they are underpowered or confounded by coincident illness, independent risk factors for dementia and surgery.[34] There is a strong need for both, adequately powered prospective and retrospective studies of the risk of AD in humans after surgery.[32,35,36] General anesthetics have benefited the society for almost two centuries and their benefits outweigh the potentially toxic effects.[34]

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