

Postoperative cognitive dysfunction and Alzheimer disease

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Abstract: Alzheimer disease (AD) is the most prevalent neurodegenerative disorder in elderly people. Patients with AD appear to be particularly at risk for cognitive deterioration following anesthesia. Some in vitro studies suggest that exposure to general anesthesia (GA) promotes the AD process. On the other hand, there are no clinical studies that clearly demonstrate that GA is a cause of cognitive dysfunction in patients with probable AD. The aim of this research was to discuss the relation between postoperative cognitive dysfunction (POCD) and AD according to the literature. In vivo studies examining AD biomarkers postoperatively and in vitro studies exploring amyloid- β (A β) converge to indicate that anesthetics could affect AD pathogenesis, either directly or indirectly. Careful evaluation of the mental state should be mandatory for all elderly patients undergoing GA. Long-term prospective, randomized clinical studies are required to examine the relationship between POCD and AD.

Key words: Anesthesia, postoperative cognitive dysfunction, Alzheimer disease

1. Introduction

There are many comorbid diseases that become more common with ageing (1). Alzheimer disease (AD), which was described by Alois Alzheimer in 1907, is the most common form of progressive, irreversible dementia in the elderly (1–3). It affects more than 25 million people worldwide; without a major therapeutic breakthrough, its prevalence is expected to increase more than 100 million by 2050 (1–5).

Worldwide, 200 million patients undergo surgery under anesthesia each year. As overall life expectancy has increased, an increasing number of elderly patients are undergoing anesthesia. In addition, elderly surgical patients are more likely to have preexisting AD or be at risk for developing it. It is well known that POCD is an important problem for the elderly and patients with probable AD (6–11). On the other hand, there are no clinical studies that clearly demonstrate that general anesthesia (GA) causes cognitive dysfunction in patients with probable AD.

This review article discusses the relationship between POCD and AD based on what we found in the currently published literature.

2. Alzheimer disease or probable Alzheimer disease

The diagnosis of AD is based on a positive history, neurological examination, and neuropsychological tests. The National Institute of Neurological and Communicative

Disorders and the Stroke-Alzheimer's Disease and Related Disorders Association Work Group criteria for diagnosing probable AD are documentation of dementia by clinical examination, deficits in two or more cognitive domains, absence of other systemic disorders, and progressive worsening of memory (12). Another commonly used criterion, according to the DSM IV (*Diagnostic and Statistical Manual of Mental Disorders*, 4th edition), is the loss of at least two of the following: orientation, memory, judgment, language, or calculation (13).

AD patients usually present with a subtle onset of memory loss, followed by slowly progressive dementia over the course of several years. The course of AD is variable, and cognitive impairment, personality change, psychotic symptoms, incontinence, gait and motor disturbances, seizures, and myoclonus may occur. Memory impairment is progressive and destructive. AD also increases the mortality of the affected population. Life expectancy varies between 4 and 8 years after diagnosis (14–22).

A definitive diagnosis of AD can be made only by autopsy of a patient's brain. This neuropathological evaluation reveals diffuse atrophy of the cerebral cortex, signifying loss of neurons. Diagnostic lesions are found on histopathological evaluation of most affected areas of the brain, which reveal the presence of large numbers of extracellular β -amyloid (β A) plaques and intracellular, neurofibrillary tangles (NFTs) (1–3,21–23). Even though plaques and NFTs are often found in cognitively normal

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elderly people, the plaques are denser and the NFTs are more widely distributed in patients with AD, according to standardized histological assessments (23).

Predisposing factors for AD are not yet fully understood. However, genes might play an important role in its development. Early-onset familial forms of AD have an autosomal dominant inheritance linked to *APP*, *PSEN1*, and *PSEN2* genes, whereas the most common sporadic form of AD, which occurs after the age of 60, has thus far been consistently associated with only the *APOE* gene (24).

Causes of sporadic AD are likely to be multifactorial (25). Numerous environmental factors have been proposed as causes of AD. One pervasive environmental factor is drug exposure. Most people receive general anesthetic agents at some point during their lives, and whether these drugs are contributing factors in the pathogenesis of AD is not clear (1–4,12,19,22,26–28).

There is a comprehensive need for treating symptoms related to AD. The most widely employed strategy is symptomatic treatment with cholinergic agents, such as acetylcholine (ACh), and monoamines, neuropeptides, and metabolic enhancers (14,16,17,19).

3. What is general anesthesia?

Around 200 million patients worldwide undergo anesthesia for major surgery every year (20). The objective of GA is to produce analgesia, amnesia, hypnosis, and muscle relaxation to facilitate surgery. Inhaled general anesthetics are highly lipid soluble and have low affinity of blood; hence they rapidly permeate the brain in high concentrations. General anesthetics and other drugs administered during anesthesia interact with the central cholinergic system (CCS). Anesthetic modulation of cholinergic transmission has profound effects on brain function via a cascade of synaptic and postsynaptic events by binding both nicotinic and muscarinic receptors. GA decreases ACh release and depression of cholinergic transmission facilitates the desirable effects of general anesthetics such as loss of consciousness, movement, pain perception, and memory. However, sometimes these effects become persistent (26,29–31). Anesthesia affects not only consciousness but also hemodynamics, thermoregulation, immunity, and pulmonary function. All these effects may adversely affect brain function. Furthermore, because of an underlying illness or condition that requires surgery, the surgery itself and its associated inflammatory process, nonanesthetic drugs, or physiology may induce postoperative cognitive problems (32).

4. Cognitive problems following anesthesia

Postoperative cognitive problems are mainly delirium and postoperative cognitive dysfunction (POCD) (6–11,13).

Delirium is defined as sudden decline in attention and focus perception, and altered level of consciousness. Onset is usually within 13 days of surgery and may last up to a week. Preoperative risk factors predisposing to delirium include aging, lower education level, reoperation, polypharmacy and drug interaction, alcohol and sedative-hypnotic withdrawal, endocrine and metabolic compromise, impaired vision and hearing, sleep deficiency, anxiety, depression, and dementia. Delirium is a common but undiagnosed complication in the elderly after major surgery. The incidence ranges from 9% to 87%, depending on both the patient and surgical conditions (33–36).

POCD is remarkably common, especially in the elderly; it can vary from mild and short-lived to severe and permanent. Immediate postoperative incidence is 10% to 25%. After several months, it can be detected in 5% to 15% (36–38). Symptoms include memory, attention, concentration, and planning problems related to executive functions. POCD is usually reported later, after the patient has left the hospital (8–11,33,38,39).

Elderly patients with dementia are at increased risk of POCD following surgery (34).

The cholinergic system is involved in cognition arousal and sensory gating. Impaired cholinergic transmission is thought to play an important role in the development of delirium. Total serum anticholinergic activity has consistently been shown to be associated with delirium in older patients. Therefore, augmentation of cholinergic function would theoretically present itself as a target for intervention with a view to reducing both the incidence and severity of delirium. There are reports of successful use of cholinesterase inhibitor to treat delirium (26,31,40).

Furthermore, anesthesia, neurotoxicity, inflammation, and stress might be conducive to POCD and delirium. Other conditions such as preexisting impairment, comorbid illness, and current events may also play a role in the development of postoperative cognitive problems. Some practitioners have reported that the type of surgery (e.g., hip fracture) and intraoperative factors (e.g., hypotension, desaturation) are contributing factors for POCD (38–42).

Assessing patients for cognitive change requires both pre- and postoperative testing. There are many tests and test batteries to determine executive functions during the postoperative period (41,42). However, there is no consensus as to the magnitude of cognitive change that should be considered clinically relevant; determination and quantification of any change require a baseline measure (38–43).

5. Cognitive dysfunction and AD

The most common postoperative complication in the elderly is POCD (33,36,38,39). Patients with AD are

considered to be particularly at risk for some of the cognitive side effects of anesthesia. Some in vitro and in vivo studies suggest that anesthetics promote and intensify the neuropathogenesis of AD (44–49). However, some researchers reported no association between anesthesia and AD (28,50–53).

Bufill et al. (54) have demonstrated an inverse correlation between the age of AD onset and cumulative exposure to anesthesia before the age of 50. Wilsoson et al. (55) have withdrawn AD biomarkers from the cerebrospinal fluid (CSF) before and after surgery and anesthesia. They also reported that CSF total tau and tau phosphorylated at Thr181 P-tau were significantly elevated following surgery, but A β 42 did not change. However, whether this was due to the surgery or the anesthesia is not clear. Similarly, Polates et al. (56) reported that a cognitive decline significantly decreased the level of β A peptides and markedly increased tau protein concentrations in the CSF of patients 6 months after cardiac surgery.

Possible mechanisms by which inhaled anesthetics could induce synaptic dysfunction and neuronal apoptosis and ultimately produce cognitive decline in the aged brain are by increasing the intracellular β A level and β A and tau aggregation and disrupting intracellular calcium homeostasis. In the amyloid and tau pathways, β -site amyloid precursor protein-cleaving enzyme (BACE) generates c-terminal fragments (CTF $_{\beta}$) from membrane-bound amyloid precursor protein. Cleavage of the CTF $_{\beta}$ by δ -secretase releases β A monomers into the cytosolic and extracellular space. Anesthetic exposure increases the levels of BACE and δ -secretase, thereby increasing the levels of intracellular β A and decreasing CTF $_{\beta}$ levels (57,58). Inhaled anesthetics also interact with the β A monomers to promote the formation of small, soluble oligomers (46). These oligomers further associate to form fibrils and extracellular plaque, which have been found to be increased in mice with transgenic AD after exposure to halothane. These effects activate caspase, initiating apoptosis and cleaving the adaptor protein GGA3, which is required for BACE lysosomal degradation. This results in increased BACE levels, further enhancing the production of β A, and introducing a vicious circle that ensures apoptosis. Microtubule (MT)-bound tau becomes

hyperphosphorylated and detached by anesthetics and hypothermia, resulting in tau aggregates and decreased MT stability. Anesthetics increase cytosolic calcium via several mechanisms. For example, inhaled anesthetics activate the endoplasmic reticulum (ER) membrane inositol 1,4,5-trisphosphate receptors (IP3Rs) and ryanodine receptors (RyRs), increasing cytosolic calcium and depleting ER calcium (59,60). These drugs also activate the sarcoplasmic/ER calcium adenosine triphosphatase (ATPase) (SERCA1), further enhancing the activity of ER calcium release pathways. Further increases in cytosolic calcium levels might be caused by activation of *N*-methyl-D-aspartate receptors and inhibition of calcium clearance via plasma membrane calcium ATPase. Increased cytosolic calcium loads the mitochondria with calcium, releasing cytochrome-c, further contributing to apoptosis. Finally, ER calcium depletion via the above mechanisms can induce apoptosis directly. Both the β A/tau and calcium pathways contribute to synaptic dysfunction and apoptotic responses (61).

Studies have indicated that POCD is associated with changes in biomarkers similar to those seen in AD (56,61).

6. Conclusion

General anesthetics and other drugs administered during anesthesia interact with the CCS, and degenerative diseases of the brain are associated with deficits in the cholinergic system. Preclinical studies exploring the impact of anesthetics on β A and tau and clinical studies examining AD biomarkers postoperatively converge to indicate that anesthetics could affect AD pathogenesis, either directly or indirectly.

Careful preoperative mental state evaluation is mandatory for all elderly patients scheduled for surgery under GA. Long-term epidemiological prospective studies (designed to control for critical variables such as type of surgery, duration of procedure, age at exposure, preexisting comorbid disease, anesthetic technique, and patient temperature) and randomized controlled trials (using biomarkers or neuro-imaging modalities) are required to examine the relationship between general anesthesia and AD to confirm such an association.

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