Aging, Anesthesia, and the Brain: Implications for You and Your Patients

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OBJECTIVES

This lecture will review new information on 1. how aging affects the brain; 2. causes and prevention of age-related postoperative cognitive impairment; and 3. implications of aging for physician performance

CASE PRESENTATION

The 2000 US Census confirms it! As a nation, we're getting older. According to the census, there were 4.2 million Americans age 85 or older in 2000, an increase of 30% since 1990, and those 75 to 84 numbered 12.4 million (vs. 10 million in 1990). Many of these people will require anesthesia and surgery. Inasmuch as the brain is the main target organ for anesthetic and adjuvant drugs, age-associated changes in the brain have important anesthetic implications for this patient population and for us as aging physicians.

THE AGING BRAIN: "NORMAL" AGING

I. Morphologic, Physiologic, and Biochemical Changes

A. Morphology.

1. Average brain weight and neuronal number inevitably decline with age1;2 beginning in young adulthood and accelerating after age 60. As a result, the ratio of brain volume to skull volume, normally about 95%, declines to about 80% in nonarians and ventricular volume triples. However, quantification of the extent of neuronal loss with age is imprecise and complicated by technical factors and substantial regional variability (e.g. prominent loss of hippocampal cholinergic neurons and cerebellar Purkinje cells). Indeed, newer data indicate the magnitude of age-related neuronal loss is much more modest than the 15% to 50% estimates of earlier studies.
2. Age also affects the business end of a neuron–the dendrites and synapses. There are age-associated decreases in neuronal size, loss of complexity of the dendritic tree, and a reduced number of synapses1;2. However, these changes are region-specific (limbic system and cortex) and may be pathological rather than normal.
3. But all is not bad. There is evidence that dendritic complexity and growth can increase in cognitively normal octogenarians2, suggesting that neuronal mechanisms crucial for learning and memory are retained in the aged but healthy CNS. In addition, counter to what many of us learned in med school, the adult brain makes new neurons and this neurogenesis continues into late old age.3 What's more, these new neurons get incorporated into memory circuits.4 As such, there is hope that enhancing neurogenesis might be a way to attenuate or reverse age-related cognitive decline.

B. Physiology.

1. The physiology of the cerebral circulation appears to be remarkably normal in the healthy aged. Absolute global CBF is decreased about 10 - 20%, not because of "hardening of the arteries", but because there is less brain mass to perfuse5. Therefore, the lower CBF is a consequence of reduced metabolic demand, not a cause of it. In general, CBF and CMRO2 remain tightly coupled in aging, autoregulation is preserved, and responsiveness to CO2 and hypoxemia are probably reasonably normal.

C. Biochemical Changes.

1 Numerous neurotransmitter systems are altered during aging6. For example, dopamine uptake sites, transporters, and levels are reduced, as are cortical serotonergic, $\alpha 2$ and $\beta 1$, and GABA binding sites. Markers of central cholinergic activity also decrease, a finding of particular significance since failure of cholinergic neurotransmission is a central feature of Alzheimer's disease7.

II. Cognitive Changes
A. Incidence.
1. Intellectual decline does not invariably accompany aging but it is common. Approximately 5% of persons over age 65 suffer from dementia, which is always a consequence of serious illness, and more subtle cognitive impairment is detectable in nearly two-thirds of all "normal" older people8. Such changes can be classified as either disease-related secondary impairment (e.g. related to alcoholism or Alzheimer's) or as primary cognitive decline. However, the line between the two is often hazy.

B. Manifestations.
1. Consistently observed changes in "normal" aging include8;9:
a. Slowed reaction time and cognitive processing. There is an inverse relationship between age and speed of motor performance. The more complex the task, the slower the response. This is due to decreased sensory sensitivity (e.g. reduced auditory acuity) as well as slowed central processing of information.
b. Deterioration in "fluid" intelligence (i.e. the ability to dynamically evaluate, accommodate, and respond to novel environmental events). However, the tests are influenced by motor speed, so slowed reaction time confounds the assessment. On nontimed tests, vocabulary, verbal information, and comprehension are well maintained. "Crystallized" intelligence (i.e. accumulated knowledge) is also relatively stable into the seventh decade of life.
c. Impaired short-term memory. Between 30 and 50% of elders report memory complaints. Much of this impairment is in working memory–which requires not only retention but also manipulation of information. Thus, the ability to store recently processed information while simultaneously acquiring new data is compromised.

C. Caveats & Exceptions
1. Having said all this, it is important to realize that the cognitive decline associated with normal aging is modest and variable10 and affected positively by physical activity and intellectual engagement.11 In fact, many active elderly individuals remain stable on measures of cognitive performance into their 80s, and even outperform younger but inactive persons on some tests8.

PATHOLOGICAL BRAIN AGING: DEMENTIA

I. Alzheimer's Disease (AD).
A. Dementia.
1. Dementia is a chronic, progressive decline in intellectual function. It can be caused by numerous systemic diseases and neurologic disorders (e.g. stroke, Parkinson's disease) but Alzheimer's disease (AD) is the most common cause of dementia and a prototype of pathological brain aging12. The diagnosis of dementia requires evidence of decline from a higher cognitive level, multiple cognitive defects, among which memory impairment is essential, and the defects must interfere with social or occupational functioning. Criteria stipulate a duration of > 6 months and, to exclude delirium, that consciousness be unaltered.

B. Diagnosis & Incidence of AD.
1. 10 - 15% of persons older than 65 years develop AD; by age 85 about 30 - 50% will be afflicted. The diagnosis is one of exclusion and requires demonstration of neurofibrillary tangles, extracellular amyloid deposits, and neuritic plaques in the brain at postmortum exam6;13;14. Growing evidence suggests these changes may be seminal events in the pathogenesis of AD and not simply markers of it15.

C. Morphologic & Biochemical Changes.
1. The brain changes seen in normal aging are present in an exaggerated form in AD. Thus, loss of brain mass occurs at a rate 2.5 times normal AD16 and hypofunction of cholinergic neurotransmission is more pronounced, particularly in areas associated with memory and cognition17. This cholinergic deficiency is a hallmark of the disease but may not, as once thought, explain the memory deficits because there is no such deficiency in the patient with mild AD18.
2. Complement mediated inflammatory responses, oxidative damage to proteins and DNA, and alterations in the hormonal milieu have been proposed as mechanisms and potential sites for future therapeutic intervention13.

D. Treatment
1. Given a deficiency in central cholinergic activity, medical therapy of AD involves using anticholineasterases such as tacrine and donepezil.17;19 Other treatments include vitamin E, steroids, and estrogen. These drugs may improve memory, attention deficits, and symptoms of AD such as apathy, agitation and hallucinations17 but, unfortunately, none seem to slow progression of AD17;20;21 and their role in prevention is unclear.
2. Perhaps the most exciting developments in treatment of AD involve newer anti-inflammatory agents and immunization against β amyloid. In fact, immunization has resulted in a marked decrease in β amyloid deposits in brain and a corresponding improvement in cognitive performance in animals, clearing the way for human trials of this novel approach.22

AGING, ANESTHESIA, AND POSTOPERATIVE COGNITIVE DYSFUNCTION

As long as 46 years ago, there was concern that some elderly patients may develop dementia following anesthesia and surgery.23 Today, that concern is justified but we're far from sure about the etiology of the problem24. Other than knowing the MAC for inhaled agents and the dose requirement for intravenous agents are decreased, little else is known about the CNS effects of anesthetics on the aging brain. The age-associated structural and functional changes described above imply, however, that the aging CNS has reduced functional reserve, perhaps making the elderly more susceptible to postoperative cognitive dysfunction (POCD).

I. Delirium
A. Definition & Incidence.
1. Delirium is an acute disturbance in consciousness and cognition that tends to fluctuate throughout the day25. It is at least twice as common in the elderly, occurring in 10-15% of elderly general surgical patients and as many as 30-50% of those undergoing orthopedic or cardiac surgery26;27. The mechanism is unknown but may be related to further decreases in already low levels of neurotransmitters such as acetylcholine. Etiologic factors include hypoxia, drug interactions (particularly anticholinergics, benzodiazepines, & tricyclics), alcohol abuse, depression, dementia, and metabolic disturbances.

B. Role of Anesthesia.
1. Several anesthetic agents can produce delirium (e.g. ketamine, benzodiazepines, and even propofol) but in the elderly the strongest association is with the anticholinergic agents atropine and scoplamine25. This is presumably because of the baseline cholinergic deficiency and suggests that with the exception of glycopyrrolate, which does not cross the blood brain barrier, medications with anticholingeric properties should be used sparingly in these patients.
2. Curiously, the type of anesthesia does not influence the risk of developing delirium. Thus, the incidence of postoperative confusion is similar regardless of whether spinal, epidural, or general

anesthesia is used28. Moreover, postoperative epidural analgesia has proven no better than the intravenous route from this point of view27.

I. Prolonged Postoperative Cognitive Dysfunction

A. Does It Exist?

1. There is now substantial evidence that it does, at least in the elderly. In a prospective, randomized trial of general versus epidural anesthesia with sedation for total knee replacement in patients > 70 years of age, cognitive performance, as assessed with psychometric tests, was worse than the preoperative baseline in 4 - 6% of them 6 months after anesthesia and surgery.28 However, the study lacked a control group for the effects of time or hospitalization alone. More convincing is a large, prospective, controlled international study29 that demonstrated a cognitive deficit in 9.9% of patients 3 months postoperatively whereas only about 3% of the age-matched controls were similarly impaired. Among patients over 75 years of age, 14% had a persistent cognitive deficit after general anesthesia and surgery.29 Moreover, these results have generally been confirmed by an ongoing study in the US30;31.
2. While such prolonged impairment is more common that previously realized, it is important to recognize that these deficits are defined by performance on psychometric tests. Whether they have social or economic significance has not been examined. Also unknown is whether the elderly are uniquely predisposed. One preliminary study suggests persistent POCD occurs in about 2% of younger patients31 but it is not clear if this is truly an effect of anesthesia and surgery since a non-operated control group was not included.

B. Does Anesthetic Technique Matter?

1. One might naturally assume that regional anesthesia is associated with a lower risk of prolonged POCD. Surprisingly, this does not seem to be the case. In elderly patients undergoing total knee replacement, for example, there was no difference between epidural and general anesthesia in the frequency of cognitive impairment 6 months postoperatively28. This is consistent with previous work indicating that shorter term postoperative (1 - 7 days) cognitive performance in the elderly is typically no better after spinal or epidural than general anesthesia, particularly if intravenous sedation is used to supplement a regional technique.32;33

C. What Causes It?

1. One old and intuitive hypothesis is that perioperative hypotension and/or hypoxia cause or exacerbate POCD. Like most simple explanations for complex problems, however, this is probably incorrect. In a large study of POCD in elderly patients29, for example, neither perioperative hypotension nor hypoxia were predictors of the cognitive decline observed 3 months postoperatively, a finding that concurs with older work34;35. Moreover, in a direct test of the influence of controlled hypotension on cognitive outcome in elderly patients under epidural anesthesia, there was no early or long-term adverse effect of hypotension (MAP 45-55 mmHg)36.
2. Emboli could be involved in some cases. For example, using transcranial doppler, cerebral emboli have been detected during total knee replacement. Whether these are biologically meaningful is unknown however.
3. The fact that the incidence of prolonged POCD is apparently similar regardless of anesthetic technique (and maybe even specific drugs37) suggests that non-anesthetic factors are likely to be important. Such non-pharmacologic contributors might include genetic factors38 and a host of physiological and social consequences of hospitalization and surgery. However, in the laboratory, we have found that isoflurane-nitrous oxide anesthesia without surgery impairs spatial learning for > 3 weeks; both young and aged rats are affected but aged animals are more susceptible.39 Accordingly, the data suggest that anesthesia itself could also be a factor in POCD.

AGING AND PHYSICIAN PERFORMANCE

What are the professional implications of CNS aging for physicians generally and anesthesiologists specifically? The answer is that we don't know, since virtually no studies have addressed this issue. There is some information, however, on a group of professionals with whom we profess some kinship–namely, pilots.

I. Aging and Pilot Performance

A. Useful Lessons From Aviation?

1. Given our propensity for drawing parallels between anesthesiology and aviation, it is instructive to consider data on age and pilot performance. First, unlike anesthesiologists, commercial airline pilots labor under age restrictions. The justification for this position is the age-related declines in sensory sensitivity, reaction time, and memory performance described above. The rule is surrounded by controversy, however, and many consider it an unjust and arbitrary policy that deprives the public of service from the most experienced pilots. In addition, evidence that older pilots manifest a "clinically important" decline in performance or are less safe than younger colleagues is far from robust.

2. Older pilots appear to do no worse than younger pilots on some challenging simulated flight tasks but may perform less well on others, suggesting that the influence of age on piloting is task specific40;41. There is also some evidence that the types of errors may vary with age. In a retrospective review of mishap records of naval aviators42, judgement errors were the main problem for younger pilots whereas older pilots made mistakes because of inattention to detail.

3. Before being too quick to extrapolate such data to anesthesiology, it is important to recognize that the definition of "old" in some of these studies is mid-30's! Indeed, a decline in specific piloting tasks can be demonstrated beginning in the 30's41, a time when many physicians are just starting rather than ending careers.

II. The Aging Anesthesiologist

A. What About Us?

1. The question–Does increasing age affect the professional performance of an anesthesiologist?–is unanswerable at present. On the one hand, there is no reason to think we are immune to the realities of aging. For example, in anesthesiologists older than about 55 years, alarm detection can be a problem because of difficulty hearing high frequency sounds (i.e. presbycusis)43 but whether this affects clinical performance is unknown. On the other hand, there is reason to believe that accumulated experience and skill creates wisdom that can negate or even supercede age-associated biologic changes44. With a population rapidly growing older and 25% of ASA members being ≥ 55 years of age (ASA Newsletter, June '01), we should have more than a casual interest in aging research. After all, not all of us will live to be old but all of us are older than we were.

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