Anesthesia, Aging and the Brain: Clinical Implications of an Evolving Science

Gregory Crosby, M.D. **Boston, Massachusetts**

The US census counted 4.2 million Americans age 85 or older in 2000, an increase of 30% since 1990. Those 75 to 84 numbered 12.4 million (vs. 10 million in 1990) and people over 85 are the fastest growing segment of the population. Many of these elders will require anesthesia and surgery. Inasmuch as the brain is the main target organ for anesthetic and adjuvant drugs, age-associated changes in brain function have important anesthetic implications and may predispose elderly surgical patients to postoperative cognitive morbidity.

"NORMAL" BRAIN AGING

Morphologic, Physiologic, and Biochemical Changes

The brain shrinks with age and undergoes widespread morphological and functional changes.(1) The ratio of brain to skull volume, which is normally about 95%, declines to about 80% in nonarians and ventricular volume triples. Some of this is due to loss of neurons but a bigger factor is loss of complexity of the dendritic tree and a reduced number of synapses.(1) Although absolute global CBF is decreased about 10 – 20% with age, this is because there is less brain mass to perfuse and reduced metabolic demand rather than "hardening of the arteries".(2) The neurochemistry of the brain also changes substantially, with decreases in most neurotransmitter systems during aging.(3) But all is not bad. Dendritic complexity and growth can increase in cognitively normal octogenarians,(2) suggesting that neuronal mechanisms crucial for learning and memory are retained in the aged but healthy CNS. Moreover, contrary to what many of us learned in medical school, the adult brain makes new neurons. This neurogenesis continues into late old age and the new neurons get incorporated into memory circuits.(4,5) These observations indicate the aged brain retains some of the plasticity that characterizes the younger brain and have important implications for maintaining or improving cognitive health. Basically, the capacity for plasticity implies the old brain should benefit from exposure to a complex environment, intellectual engagement, and physical exercise. Evidence supports this concept, although more so for the value of being physically active than doing the cross-word puzzle.(6) The point is that some aspects of brain aging may be modifiable and that the "use it or lose it" adage is apt even—or especially—for the brain! (Wall St. Journal, Mar. 3, 2006, B1)

Cognitive Changes

What does all this mean for brain function? Intellectual decline does not invariably accompany aging but it is common. Approximately 5% of persons over age 65 suffer from dementia and more subtle cognitive impairment is detectable in nearly two-thirds of all "normal" older people.(7) The old brain is slower to process information and slower to react; the more complex the task, the slower the response.(8) The old brain is also less agile, meaning it doesn't handle simultaneous tasks as well, reflecting deterioration in short-term working memory (i.e. the ability to process, evaluate, and retain information while simultaneously acquiring new data). However, vocabulary, comprehension, and "crystallized" intelligence (i.e. accumulated knowledge) are relatively stable into the seventh decade of life. That said, it is important to realize that the cognitive decline associated with normal aging is modest and variable. Moreover, as mentioned earlier, it is influenced in a positive way by physical activity and perhaps intellectual engagement.(9) 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 tests.(7,8) Consequently, there is no such thing as a "typical" older person, making studies of this population difficult because chronological age is not a reliable predictor of cognitive ability.

PATHOLOGICAL BRAIN AGING: ALZHEIMER'S DEMENTIA

Dementia is a chronic, progressive decline in intellectual function. Alzheimer's disease (AD) is both the most common cause of dementia and a prototype of pathological brain aging.(10) It is also frighteningly common. Ten – 15% of persons older than 65 years develop AD; by age 85, about 30 - 50% will be afflicted. Brain changes seen in normal aging are present in an exaggerated form in AD. Thus, with AD, loss of brain mass occurs at a rate 2.5 times normal(11) and hypofunction of cholinergic neurotransmission is more pronounced, particularly in areas associated with memory and cognition. 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 AD.(12) The leading hypothesis as to the cause of AD centers on an imbalance between generation and clearance of β amyloid (βA), a protein produced by proteolytic cleavage of a larger precursor, amyloid precursor protein (APP). Accumulation of amyloid plaques is an early pathological feature in the brain of asymptomatic carriers of gene mutations that predispose to development of AD and plaques are widespread in late stage AD. Moreover, βA itself appears to

contribute to synapse loss and dysfunction even before deposits are detected.(13) Despite much improved understanding of the pathogenesis of AD, however, there is as yet no "magic bullet" for this disease. Current treatments modify the symptoms but do little to slow progression of AD. Anticholineasterases such as tacrine and donepezil are still the mainstay of treatment(12) but vitamin E, steroids, and estrogen also have advocates.(14,15) Such treatments may improve memory, attention deficits, and symptoms of AD such as apathy, agitation and hallucinations but the results are inconsistent.(15) In contrast, considerable current work focuses on prevention and/or treatment of AD by lowering the amyloid burden. In this respect, some NSAIDS (ibuprofen but not naproxen or aspirin) decrease β amyloid production(16) and a few small studies suggest regular use of them reduces the risk of developing AD. Immunization against βA works well in animals but an encephalitic reaction to the antigen has occurred in some patients(14); this has not dampened enthusiasm for this approach, just prompted a search for antigens with fewer adverse effects. Finally, APP cleavage enzymes and adaptor proteins are targets of active investigation with the hope that pharmacological modulation of processes involved in βA production and elimination will prove in the future to be an effective treatment or preventative tactic.

POSTOPERATIVE COGNITIVE DYSFUNCTION (POCD)

It was first argued 50 years ago that some elderly patients develop dementia following anesthesia and surgery.(17) Concern that the elderly brain "takes a hit" during general anesthesia and surgery is better justified today but we're still far from sure about the etiology and significance of the problem(18), mainly because we know so little about how the old brain responds to these events. The age-associated structural and functional changes described above imply, however, that the aged CNS has reduced functional reserve, which may explain why the elderly are more vulnerable to development of persistent POCD.

Delirium

Delirium, an acute disturbance in consciousness and cognition that tends to fluctuate throughout the day, is the most common form of perioperative CNS dysfunction.(19,20) It is 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 surgery.(21) The mechanism is unknown but one hypothesis is that it may be related to further decreases in already low levels of neurotransmitters such as acetylcholine. Etiologic or predisposing factors include hypoxia, drug interactions (particularly anticholinergics, benzodiazepines, & tricyclic antidepressants), alcohol abuse, pre-existing depression or dementia, and metabolic disturbances. Delirium is more than an annoyance; it is associated with longer hospital stay, higher mortality, and may even be a marker for subsequent development of dementia.(22,23) The role of anesthesia in development of perioperative delirium is complex. Certain anesthetic agents (i.e. ketamine, benzodiazepines, propofol) can produce delirium, as can drugs with anticholinergic activity if they cross the blood brain barrier (e.g. atropine, scopolamine).(24) Curiously, however, the incidence of postoperative confusion appears to be similar with spinal, epidural, and general anesthesia, with and without nitrous oxide.(25,26) Moreover, postoperative epidural analgesia has proven no better than the intravenous route from this point of view(27); the effectiveness of pain management appears to be more important than the specific agents used.(28)

What can be done about perioperative delirium? First, identify patients at high risk(29) and avoid or minimize some of the medications just mentioned. Second, consider obtaining a preoperative geriatric consultation since there is some evidence that a perioperative re-orientation program markedly reduces the incidence of delirium, particularly in high risk patients.(30) Third, although many factors contributing to delirium are not modifiable (e.g. age of patient, type of surgery), it is important to identify and manage remediable causes such as pain, hypoxemia, and sepsis. Lastly, when prevention fails, one can manage the symptoms pharmacologically, although this too is controversial.(20)

Prolonged Postoperative Cognitive Dysfunction

Many elderly patients experience cognitive deterioration postoperatively. The most convincing evidence in this regard comes from a large, prospective, controlled international study(31) that demonstrated a cognitive deficit in 9.9% of elderly patients 3 months postoperatively whereas only about 3% of the age-matched controls (not hospitalized, no surgery) were similarly impaired. Among patients over 75 years of age, 14% had a persistent cognitive deficit after general anesthesia and surgery.(31) Postoperative cognitive impairment is not unique to the elderly—it occurs in middle-aged patients too(32)—but it lasts longer in elders. The social and economic

significance of the impairment has not been well examined but it is clear that prolonged postoperative cognitive impairment is real and more common than previously recognized. The good news is that patients seem to recover completely within 1-2 years or less, but this optimism is based on follow up of only a small subgroup.(33)

The key question, of course, is what causes it? The short answer is that no one is certain. One old and intuitive hypothesis is that perioperative hypotension and/or hypoxia cause or exacerbate POCD. Like most simple explanations for complex problems, this is probably incorrect in most cases. In fact, the large international study of POCD referred to earlier(31) found that neither perioperative hypotension (MAP < 60% for ≥ 30 min) nor hypoxia ($SpO_2 \leq 80$ for > 2 min) were predictors of cognitive decline 3 months postoperatively. Moreover, in a direct test of the influence of controlled hypotension on cognitive outcome in elderly patients under epidural anesthesia, no early or long-term adverse effect of hypotension (MAP 45-55 mmHg) was observed.(34) There could be some patient or procedure – specific causes or risk factors for POCD. The role of pre-existing cognitive status is unknown since patients with poor cognitive performance at baseline have been excluded from the trials performed to date. The complexity and duration of surgery may play a role since the incidence is lower following outpatient procedures. Emboli could be involved in some cases; cerebral emboli have been detected during total knee replacement using transcranial doppler.(35) Genetic predisposition is also feasible but the only study thus far looked at apo E4, a susceptibility gene for Alzheimer's disease, and found no association with POCD.(36,37) Finally, the stress, immobility, social isolation, and/or inflammation associated with having surgery could be involved but no studies have directly investigated these possibilities.

One factor that is receiving greater attention is general anesthesia itself. There are many reasons to speculate that general anesthesia might contribute to POCD, not the least of which is that anesthesia is obviously a profound form of CNS dysfunction. However, clinical evidence for this is sparse. First, most data indicate the risk of prolonged POCD is similar with regional and general anesthesia. Thus, in elderly patients undergoing total knee replacement, the frequency of cognitive impairment 6 months postoperatively was similar (4 – 6%) between the epidural and general anesthesia groups.(25) However, intravenous sedation was used to supplement the regional technique and patients also had a surgical procedure, making it difficult to isolate the influence of anesthesia itself. A more recent study suggested that the incidence of POCD 1 week after surgery was higher after general anesthesia but the study was underpowered and there were no differences between the regional and general anesthesia groups 3 months later.(38) In the laboratory, however, we have found that isoflurane-nitrous oxide anesthesia without surgery impairs spatial learning for weeks in aged rats.(39) Because the agents are long cleared from the brain by the time behavioral testing is begun, these data imply that the neurobiological machinery of memory is somehow altered in an enduring way by anesthesia itself. Supporting this concept, we have found changes in gene expression in the hippocampus, a region important for spatial learning, in old rats 2 d after isoflurane-nitrous oxide anesthesia.(40) Anesthetic-induced neurotoxicity may also be a factor. Apoptotic neurodegeneration occurs in cell culture after exposure to clinically relevant dosages of isoflurane(41) as well as in the brain of old rats after nitrous oxide and ketamine(42). Isoflurane also increases oligomerization and toxicity of β amyloid(43) and increases activity of the APP cleavage enzyme β secretase in cell culture.(41,44) Accordingly, there is a possibility that general anesthesia, either by changing or damaging the old brain, could be a factor in POCD.

Because the mechanisms of POCD are still uncertain, it is difficult to recommend specific prevention or treatment strategies. In particular, other than recognizing that elders are often cognitively fragile and treating them accordingly, there is presently no scientific basis for recommending (or avoiding) a specific anesthetic agent or technique on the basis of concerns about POCD. This will hopefully change with further research but, in the meantime, it is reassuring that the prognosis for recovery from POCD appears to be good.

AGING AND PHYSICIAN PERFORMANCE

Does age and experience make us better physicians or worse? The question is difficult to answer but it is becoming a hot topic of discussion and debate. Consider the airline industry. Commercial airline pilots labor under age restrictions; the U.S. kicks them out of the cockpit before they reach their 60th birthday. Evidence that older pilots manifest a "clinically important" decline in performance or are less safe than younger colleagues is weak, however, and the rule is currently being challenged (Wall St. Journal, Feb. 22, 2005).

Physicians, like airline pilots, are not immune to the realities of aging. Measures of IQ decline at the same rate in MDs and non-MDs with age and presbycusis among anesthesiologists older than about 55 years may make alarm detection problematic.(45) But do these mean anything for actual professional performance? There is evidence from

internists / family practitioners, albeit “soft”, for an inverse relationship between age and competence.(46) This has been attributed to a relative lack of attention to detail in the older MDs, which is consistent with the known age-related decrement in analytical processing and increased reliance on ‘gist’ and intuition. But gist and intuition improve with age. Indeed, the diagnostic accuracy of older primary care MDs appears to be better than that of younger colleagues, supporting the widely held view that the ‘wisdom of age’ negates or even supersedes age-associated biologic changes (“practice makes perfect”)(47). The bad news is that intuition and gist may not be ideal problem solving methods because they often generate incorrect hypotheses, particularly in a complex situation.(46) This tension between the relative merits of a younger versus older physician is highlighted by a recent systematic review of studies examining the relationship between health care quality and physician age and years in practice (48). In more than half of the studies reviewed, physician performance declined with years since graduation from medical school. Most of the studies reviewed used as the performance measure knowledge tests or adherence to standards of practice, diagnosis, or treatment (i.e. willingness to follow the “rules”). Disturbingly, however, in all but one of the studies that used actual patient events as the outcome measure (e.g. mortality from acute MI, perioperative mortality of coronary artery bypass surgery) the association between age / years in practice and poorer outcome held up.

This report can be criticized legitimately on several levels (e.g. retrospective nature, somewhat arbitrary reasons for including or excluding studies, reliance on adherence to standards rather than actual patient outcomes) but nevertheless has already generated attention grabbing headlines (“Greater Risk Seen With Older Doctors“, Boston Globe, Feb. 15, 2005). We will increasingly be challenged to look carefully at ourselves and our colleagues, even though we may already do this informally. A survey of practicing anesthesiologists revealed that many made changes in their professional lives as they got older, such as working fewer hours and avoiding complex cases.(49) Notably, adjustments were for the most part self-initiated rather than externally imposed. Whether this reflects a change in the ability or desire to perform at previous levels is unclear but, with 27% of ASA members ≥ 56 years of age and 30% between 46 and 55 years (ASA Newsletter, June ’05), it is a subject that should interest us all.

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