Surgery Has More Profound Effect Than Anesthesia On Brain Pathology

A syndrome called “post-operative cognitive decline” has been coined to refer to the commonly reported loss of cognitive abilities, usually in older adults, in the days to weeks after surgery. In fact, some patients time the onset of their Alzheimer’s disease symptoms from a surgical procedure. Exactly how the trio of anesthesia, surgery, and dementia interact is clinically inconclusive, yet of great concern to patients, their families and physicians.

A year ago, researchers at the Perelman School of Medicine at the University of Pennsylvania reported that Alzheimer's pathology, as reflected by cerebral spinal fluid biomarkers, might be increased in patients after surgery and anesthesia. However, it is not clear whether the anesthetic drugs or the surgical procedure itself was responsible. To separate these possibilities, the group turned to a mouse model of Alzheimer’s disease. The results, published online this month in the *Annals of Surgery,* show that surgery itself, rather than anesthesia, has the more profound impact on a dementia-vulnerable brain.

The team, led by Roderic Eckenhoff, MD, Austin Lamont Professor of Anesthesia, exposed mice with human Alzheimer disease genes, to either anesthesia alone, or anesthesia and an abdominal surgery. The surgery was similar to appendectomy or colectomy, very common procedures in humans. They found that surgery causes a lasting increase in Alzheimer’s pathology, primarily through a transient activation of brain inflammation. Also, a significant cognitive impairment persisted for at least 14 weeks after surgery compared to controls receiving anesthesia alone. Neither surgery nor anesthesia produced changes in normal non-transgenic animals.

“In the mice, there was a clear and persistent decrement in learning and memory caused by surgery as compared with inhalational anesthesia – but only in the context of a brain made vulnerable by human Alzheimer-associated transgenes,” notes Eckenhoff.

He also notes that at the time of surgery, the AD mice showed no outward symptoms of AD, despite having subtle evidence of ongoing neuropathology. “This timeline is analogous to both the age range and cognitive status of many of our patients presenting for a surgical procedure and suggests the window of vulnerability to surgery of the Alzheimer’s brain extends into this pre-symptomatic period,” says Eckenhoff. This period might be analogous to what is now called prodromal AD.

“On the other hand,” cautions Maryellen Eckenhoff, PhD, a neuroscientist on the team, “the brain vulnerability seen in the AD mice may not translate well to people.” The AD mice used, like all current mouse models of Alzheimer disease,

more closely resemble the situation in familial Alzheimer disease, which constitutes only a small minority of patients. She points out that it is not yet clear whether results from AD mouse models will represent patients who eventually get late-onset, or “sporadic” Alzheimer disease. These mice are, however, the current standard of choice for screening new drugs and have yielded considerable insight into Alzheimer pathogenesis.

The mechanism linking surgery and the cognitive effects seems to be inflammation. An inflammatory process is well known to occur as a result of surgery, at least outside the central nervous system. How this inflammatory process gains access to the brain, and accelerates AD pathology in a persistent way is still unclear. Post-operative cognitive decline has not been convincingly demonstrated to persist after three months in most people, and whether it predicts later dementia is still unclear. This study suggests that in the setting of a vulnerable brain, the cognitive deficits after surgery might be irreversible.

However, the finding that inflammation is the underlying mechanism immediately suggests a strategy for mitigating injury. “Human studies will be needed to first confirm these findings and then begin to deploy anti-inflammatory strategies to minimize injury,” adds Eckenhoff. “As a profession, doctors need to understand the long-term implications of our care, both positive and negative, and do all we can to delay the onset of dementia.”

Co-authors, all from Penn, are Junxia X. Tang, Feras Mardini, Luke S. Janik, Sean T. Garrity, Rosie Q. Li, and Gulnaz Bachlani. This study was funded by the National Institute on Aging and the Austin Lamont Endowment Fund.

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