Neuroinflammation may be behind general-anesthesia-associated learning disabilities

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Several studies have found evidence that children who undergo repeated surgical operations with general anesthesia before the age of 4 may be at an increased risk for learning disabilities. In the March issue of *Anesthesiology*, Massachusetts General Hospital (MGH) researchers report an animal study indicating that several factors – age, the specific anesthetic agent used and the number of doses – combine to induce impairments in learning and memory accompanied by the inflammation of brain tissue. An accompanying paper from the same team finds that the offspring of mice that received a specific anesthetic gas during pregnancy also showed the effects of neuroinflammation and impaired learning. Both articles have been released online.

"We found that different anesthetic drugs – sevoflurane but not desflurane – had different effects on neuroinflammation and on learning and memory function in young mice," says Zhongcong Xie, MD, PhD, corresponding author of both studies and director of the Geriatric Anesthesia Research Unit in the MGH Department of Anesthesia, Critical Care and Pain Medicine. "If they are confirmed by future studies in animals and humans, these findings would suggest that some anesthetics may be safer than others in young children and indicate ways to reduce risks."

In the first study – co-led by Xia Shen, MD, PhD, and Yuanlin Dong, MD, MS, both of MGH Anesthesia – the investigators treated two groups of 6-day-old mice with sevoflurane, the most commonly used general anesthetic. One group received a single two-hour dose of the

drug, while the other received the same dose on three subsequent days. In a standardized assessment of learning and memory conducted 24 days later, the mice that had received three doses did significantly less well than a control group at learning the location of a platform in a shallow pool of water and then remembering where the platform had been after it was removed. Analysis of their brain tissue showed elevated levels of several markers of inflammation.

Mice that received only one dose of sevoflurane showed neither neuroinflammation nor cognitive impairment compared with the control group. No adverse effects were seen in either adult mice that received three doses of sevoflurane or in young mice that received three doses of desflurane, another commonly used anesthetic. Two strategies – preanesthesia treatment with an anti-inflammatory drug and placing the young animals in an enriched environment – cages that featured ladders, wheels and mazes – each appeared to reduce the negative effects of three doses of sevoflurane.

The second study – co-led by Hui Zheng, MD, PhD, of MGH Anesthesia and Dong – exposed a group of pregnant female mice to a single two-hour dose of sevoflurane when two-thirds through the gestation period. In assessments conducted 30 days after the females gave birth, offspring of those that received sevoflurane showed evidence of impaired learning and memory, compared with a control group. In addition, analysis of the brain tissue of fetal mice, taken right after the pregnant mice received the sevoflurane dose, and of month-old offspring showed elevated inflammatory markers and other signs of neurotoxicity – including a reduction in the number of brain synapses – compared with control offspring. As in the first study, placing a group of anesthesia-exposed pregnant mice and then their offspring into an enriched environment appeared to reduce both the neuroinflammatory and behavioral effects on the offspring of prenatal exposure to sevoflurane.

"Six million children undergo surgery each year in the U.S., and the possibility that anesthesia and surgery could increase the risk for learning disabilities is a major concern for both the medical community and the general public," says Xie, an associate professor of Anesthesia at Harvard Medical School. "We hope our findings will promote more research into anesthesia neurotoxicity in the developing brain, ultimately leading to safer anesthesia care and better postoperative outcomes for children." Support for both studies includes grants R21AG029856, R21AG038994, R01GM088801 and R01AG041274 from the National Institutes of Health, along with grants from the Alzheimer's Association and the Cure Alzheimer's Fund and support from the MGH Department of Anesthesia, Critical Care and Pain Medicine.

Provided by Massachusetts General Hospital

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