Anesthesia Exposure and Neurotoxicity in Children—Understanding the FDA Warning and Implications for the Otolaryngologist

Over the past decade, a large body of evidence has suggested that there may be an association between anesthesia exposure and neurocognitive deficits in children. The majority of data are derived from animal studies, but some human studies support an association between single or multiple anesthesia exposures in young children and cognitive deficits.1 With the exception of a recent prospective study and a recent ambidirectional study,2,3 human studies are limited to retrospective cohort studies that lack adequate controls or attention to the impact of confounding variables. On December 14, 2016, the US Food and Drug Administration (FDA) issued the warning that “repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women during their third trimester may affect the development of children’s brains.”4

This warning will result in a label change for 11 common general anesthetics and sedative agents that are thought to act through y-amino butyric acid type A or N-methyl-D-aspartate class of glutamate receptors. This label change will include all anesthetic gases, such as sevoflurane, and intravenous agents such as propofol, ketamine, barbiturates, and benzodiazepines.

The aim of this article is to inform the otolaryngology community about the implications of this recent FDA warning. We also suggest some practical changes to the informed consent process and summarize the available data needed to counsel families who may have concerns.

Preclinical Studies
Anesthesia-induced neurotoxicity was highlighted in the seminal work by Jevtovic-Todorovic et al.5 These investigators reported that 7-day-old rats exposed to a combination of isoflurane, nitrous oxide, and midazolam developed apoptosis, impaired synaptic function, and memory deficits. The development of neurotoxicity after exposure to common anesthetics has been subsequently confirmed in different species, such as roundworms, mice, rats, guinea pigs, and nonhuman primates. The neurotoxic effect depends on the animal’s stage of development, medication dose, and duration of exposure to the anesthetic.

Some researchers believe that general anesthetics can induce activation of nerve cell apoptosis by disrupting intracellular calcium hemostasis in a time-, concentration-, and species-dependent pattern.5 Furthermore, some studies in nonhuman primates, including a recent study on infant rhesus macaques,6 have confirmed anesthesia-induced neurotoxicity resulting in negative cognitive effects and histologic confirmation of brain atrophy. These findings raise concerns about the implications of anesthesia exposure early in life and long-term cognitive consequences in humans.

Clinical Studies
Various retrospective cohort studies have shown conflicting results. Some studies conclude that multiple anesthesia exposures are a significant risk factor for the development of learning disabilities, whereas other studies report no such association.7

The Pediatric Anesthesia and Neurodevelopment Assessment (PANDA) study,2 a multicenter, ambidirectional, sibling-matched cohort study, included neuropsychological assessments in 1035 sibling pairs. Only one sibling was given general anesthesia for a herniorrhaphy procedure performed within the first 3 years of life. No significant difference was noted in any of the neuropsychometric measures assessed between the exposed and unexposed siblings at the ages of 8 through 15 years.

The General Anesthesia and Spinal (GAS) study8 is a prospective, multi-center, randomized clinical trial of 722 children younger than 60 weeks. The children were scheduled for a hernia repair procedure and were randomized to awake-regional anesthesia or sevoflurane general anesthesia. Although the primary end point was not reached (a 5-year primary end point is expected in 2018), Davidson et al9,10,11,12,13 reported “no evidence that less than 1 hour of sevoflurane anesthesia in infancy increases the risk of adverse neurodevelopmental outcome at 2 years of age compared with awake regional anesthesia.”

Although an animal study14 reported an association between anesthesia exposure and cognitive deficits, most human studies2,3,15 have failed to replicate these findings. Results are mixed, possibly owing to differences in study design, outcomes measures, age at assessment, length of anesthesia, and comorbid conditions. It is difficult to isolate the effects of the underlying disease and the surgery itself from the effects of anesthesia. The PANDA and GAS studies also examined brief, single episodes of anesthesia exposure, whereas the animal studies that showed neurotoxicity involved either prolonged or multiple anesthesia exposures. There may be justifiable concerns that multiple or prolonged use of anesthetics may be associated with adverse cognitive effects. We expect well-designed studies to report results later this year.

As a result of the recent FDA warning, pediatric anesthesiologists and otolaryngologists may be unsure about the correct approach to counsel families with children younger than 3 years who require surgery. Many op-
All otolaryngologists who operate on children younger than 3 years should be aware of the FDA warning and have a plan to manage its implications. Otolaryngologists perform some of the most common procedures for children younger than 3 years, and these procedures may be repeated on multiple occasions for recurrent symptoms. An otolaryngologist should balance the risk of anesthesia that may lead to cognitive deficits against the long-term effects of multiple ear infections, intermittent hearing loss, airway disorders, and sleep-disordered breathing, which can lead to intermittent hypoxia, multiple arousals, and behavioral problems. One approach to remedy this problem is to discuss the FDA warning before surgery with parents of all children younger than 3 years who would be receiving an anesthetic. This approach allows an opportunity for shared decision-making and provides additional information about the duration of anesthesia, the likelihood of needing various general anesthetics for multiple procedures, and the possibility that the procedure could be delayed until after the child becomes 3 years of age. Written and online information may be provided to parents. This approach will be time consuming but comprehensive and may need to be modified in light of new information from ongoing clinical trials. Because the anesthesiologist meets the family relatively late in the administrative process, the otolaryngologist should start the discussion of anesthetic risks before scheduling the procedure. At least one major pediatric hospital has adopted this strategy.9

REFERENCES