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Anesthetics and Cognitive Impairments in Developing Children:

What Is Our Responsibility?

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For decades, a variety of general anesthetics and sedatives have been used in pediatric medicine with the goal of providing safe and effective care to children during painful and/or uncomfortable procedures. This practice was believed to be innocuous until animal research over the past 20 years brought an uncomfortable realization to our attention: commonly used general anesthetics and sedatives may have a detrimental effect on immature brain development with long-lasting consequences on cognitive and behavioral outcomes.

A decade-long debate regarding the relevance of animal findings to clinical practice has reached a new level owing to the public warning issued by the US Food and Drug Administration (FDA) in December 2016. Namely, the FDA advises health care professionals to “balance the benefits of appropriate anesthesia in young children and pregnant women against the potential risks, especially for procedures that may last longer than 3 hours or if multiple procedures are required in children under 3 years.”¹ Importantly, the FDA suggests that the timing of procedures that necessitate anesthetic and sedation drugs should be discussed with families and caregivers. As a result, many academic institutions have chosen to include a discussion about the potential for anesthesia-induced impairments of brain development in the informed consent. Interestingly, the FDA goes on to urge not only medical professionals, but also parents and caregivers, to report adverse events “involving anesthetic and sedation drugs...to the FDA MedWatch program.”¹

As we are faced with this compelling announcement, the validity of these concerns is being questioned. Having been in the field of anesthesia-induced developmental neurotoxicity since its conception, I am impressed with the overwhelming and highly reproducible animal evidence that has been presented over the past 20 years. We have come a long way from the early observations in rodent studies² that brought to our attention a real possibility that general anesthetics may cause harm to a young brain. The rapidly growing body of evidence coming from nonhuman primate studies^{3–5} confirms the findings of the rodent studies and takes concerns to the next level. General anesthetics are now recognized as powerful modulators of neuronal and glial development in the mammalian brain and not as innocuous agents that only put children to sleep and make them insensitive to pain.

Numerous morphologic studies have suggested that developmental neuroapoptosis, a normally occurring phenomenon that allows for pruning of redundant neurons and glial cells

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during active stages of brain development, is significantly enhanced by general anesthesia.^{2,3} It is believed that general anesthetics do not introduce a unique type of cell death but rather promote excessive and uncontrolled activation of the existing apoptotic machinery. Of interest is that a glial cell line, oligodendrocytes, responsible for myelination of neuronal axons, are particularly vulnerable to anesthesia-induced damage.³ This suggests that anesthesia causes complex damage to the developing neurons, not only by triggering their apoptotic death, but by disturbing timely axonal myelination as well.

These morphologic disturbances appear to have far-reaching consequences related to neuronal functioning, timely and proper neuronal network formation, synapse formation, and stabilization.^{2,6} Those faulty neuronal circuitries may be a morphologic and functional correlate of the behavioral deficiencies reported in rodents and monkeys exposed to general anesthesia during the critical stages of their brain growth spurt.

Namely, when the development of cognitive abilities of animals exposed to general anesthetics at the peak of synaptogenesis were examined, they lagged behind those of controls.^{2,4,5} It was suggested that not only a single, longer exposure could lead to cognitive deficits,^{2,4} but that multiple, shorter-lasting exposures to anesthesia during vulnerable periods can also cause significant impairments in learning, psychomotor speed, concept formation, and motivation, with reports of a higher frequency of anxiety-related and affiliative/appeasement behavior.⁵ This suggests cognitive as well as socioemotional disturbances.

Animal research notwithstanding, the relevance of these findings to daily clinical practice remains unclear. Should we consider the mounting evidence in nonhuman primate research to be irrelevant despite the fact that the development of the monkey brain is very similar in timing, duration, and complexity to the development of the human brain? I do not think so, particularly when we evaluate the emerging clinical evidence that maintains the viability and credibility of these concerns.

Current clinical findings show a robust association between an early exposure to anesthesia and learning disabilities/behavioral impairments later in life,⁷⁻⁹ in particular when the exposure was prolonged and/or repeated. For example, in a cohort of 1036 patients, anesthesia exposure lasting more than a couple of hours or multiple exposures occurring before age 3 years resulted in a higher propensity for developing learning disabilities and attention-deficit/hyperactivity disorder.⁷ In particular, multiple exposures were associated with decreased cognitive ability and academic achievement, whereas single exposures were associated with modest decreases in reading and language achievement but not cognitive ability.⁷ A retrospective study looking at otherwise healthy children who were exposed to anesthesia before age 1 year reported that about 12% to 14% performed below the fifth percentile on academic achievement tests compared with the population as a whole (about 5%).⁸ The study suggests a direct correlation between the length of exposure and learning disabilities (ie, the longer the duration of anesthesia, the lower the scores on academic achievement tests), but the authors caution that there may be explanations other than anesthesia exposure.

Although very early stages of brain development suggest higher vulnerability, a 2014 epidemiologic study⁹ suggests that children exposed to a general anesthetic between ages 3 and 10 years may also be vulnerable. The authors report that children who are exposed to anesthesia have a higher propensity to develop motor deficits, even when comorbidities or earlier injuries were taken into consideration without significant effects on language or cognitive abilities. Thus, developmental milestones may be affected in complex ways by exposure to anesthesia at different developmental stages.

A 2016 randomized clinical trial examined outcomes after a relatively brief exposure (less than an hour) in infancy to either general or awake regional anesthesia.¹⁰ The cognitive composite scores of children in both groups, when tested at age 2 years using the Bayley Scales of Infant and Toddler Development–Third Edition, were comparable, thus confirming previously published findings that brief exposure to general anesthesia may not be detrimental to cognitive development.¹⁰ However, it remains to be determined whether cognitive and/or behavioral development is impaired when assessed at an older age.

As we continue to scrutinize the importance of anesthesia-induced cognitive and behavioral impairments, we face a dilemma of how to proceed. Many approaches have been considered, such as ignoring it or making substantial changes in daily clinical practice (eg, taking a conservative instead of surgical approach, postponing the surgical procedure to a later date, shortening and/or minimizing the repeated exposures, combining general anesthetics with safening agents, or developing safer anesthetic drugs). Whatever approach we take, this dilemma cannot be ignored and, as such, requires relentless pursuit of truth through rigorous scientific inquiry so that we can continue to responsibly serve our youngest patient population.

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