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The Pediatrician and Anesthesia Neurotoxicity

Confusion now hath made his masterpiece.
William Shakespeare[1]

The evolution of safe and effective pediatric anesthesia care has been one of modern medicine's greatest achievements. By all currently available clinical measurements, anesthesia and sedation in healthy children are extraordinarily safe and have enabled children worldwide to undergo millions of surgical, diagnostic, and therapeutic procedures each year. However, anesthesia researchers are now focusing on the disquieting notion that administration of an apparently uncomplicated general anesthetic in an otherwise healthy child may lead to later cognitive or behavioral deficits. The report by Flick et al[2] in this month's issue of *Pediatrics* brings this dilemma to the attention of the pediatric community. The clinical significance of anesthetic neurotoxicity is controversial and under heated debate.[3–6] However, from this point forward, pediatricians must be an intimate part of the discussion. As the primary drivers of most surgical and diagnostic procedures, pediatricians will have to assess whether the benefits of these procedures justify the purported but completely unquantifiable risk of the anesthetic or sedative. In addition, this issue has already become popular in the media, and as our experience with the supposed links between autism and vaccinations has demonstrated, this is likely to be a confusing and potentially inflammatory issue with the lay public as well.

An increasing volume of nonhuman research over the past decade has established a relationship between the administration of general anesthetics and sedatives during periods of rapid brain growth and an increase in neuronal apoptosis and subsequent long-term behavioral impairment. All of our most commonly used anesthetics and sedatives, notably including midazolam and propofol, have been implicated.[7–9] Local anesthetics and narcotics seem to be free of concerns.[10] Translation of these observations to humans has proven much more difficult, and the clinical relevance remains uncertain. Currently available human studies have been necessarily retrospective. Although a number of studies have found an association between the administration of anesthesia and surgery and subsequent cognitive or behavioral deficits, other studies have failed to do so.[11–14] Multiple confounders, including the combined effects of both anesthesia and surgery, age at exposure, comorbid conditions, and historical differences in anesthetic agents and monitoring, make it extraordinarily difficult to isolate the effects of general anesthesia alone.

Flick's group[2] at the Mayo Clinic took advantage of a database unique to Olmsted County, Minnesota. Their study builds on previous work by their group in which health records (including anesthetic and surgical records) were linked with school-performance data.[11] Their conclusions indicate an association with 2 or more episodes of anesthesia

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and surgery and the subsequent development of learning disabilities. No association was seen after the administration of a single anesthetic and surgery. Because deficits in memory and learning are the areas of interest predicted by much of the preclinical animal work, it is intriguing that Flick et al[2] found a specific association between exposure and the diagnosis of learning disabilities and the need for an individualized educational plan based on difficulties in learning. No relationship was established between exposure and the need for an individualized educational plan based on emotional and behavioral issues. Although their results are provocative, it is important to note that this type of retrospective epidemiologic approach necessarily suffers from the limitations mentioned previously. Although the authors controlled for burden of illness as best as was practical, it is not possible to completely isolate the need for surgery and any potential effects of the surgical procedure from the effects of the anesthetic per se. The clinical significance of these limitations remains subject to vigorous debate.

Pediatricians should be intensely interested in this new work for a number of reasons. Taken in sum, the Mayo group's reports[2,11] suggest an association between the use of multiple anesthetics and surgical procedures and the subsequent development of learning disabilities, and there was a possible dose-response curve. Because few children undergo more than a single surgical procedure in the first few years of life, a modicum of reassurance can be obtained by the failure to reveal any discernible clinical effects after a single exposure. However, because the study occurred in the relatively homogenous population of Olmsted County, it is uncertain if there are subgroups of children who would potentially be at more (or less) risk after a single anesthetic and surgery. Children may also have a higher rate of exposure to anesthetic and sedative agents than initially appreciated. Pediatricians increasingly refer children for procedures that require sedation (eg, MRI, endoscopy, vascular access). The sedation required for these procedures typically involves use of agents of concern and may occur repeatedly or in preparation for a subsequent anesthetic for surgery.

An aggressive effort is underway to fully understand the clinical significance of anesthetic neurotoxicity. The US Food and Drug Administration and the International Anesthesia Research Society have formed a unique public-private partnership entitled SmartTots (smarttots.org), and several prospective human trials are underway.[15–17] It is unfortunate that, because of the delay required for recruitment of patients into these studies and the subsequent time lag before any clinical effects become measurable, definitive results are still years away. Even then, these studies are only able to examine the effect of a single, relatively brief exposure to surgery and anesthesia. A well-designed comprehensive study to examine the effects of multiple episodes of surgery, anesthesia, and sedation seems to be many years away at best and, perhaps ultimately, impractical. Consequently, we are likely to be living with some degree of uncertainty on this issue for the indefinite future.

While we wait for more definitive answers, pediatricians should verse themselves on this subject and can expect questions from anxious parents seeking answers or alternatives. A subset of procedures (including inguinal hernia repair, circumcision, etc) can be safely and efficiently conducted under a regional anesthetic technique such as spinal anesthesia.[18,19] Because regional anesthesia seems to be free of risk from neurotoxicity, this option should be explored with the surgical and anesthetic team in appropriate cases.[10] However, most surgical procedures will require general anesthesia, and neither surgery nor anesthesia should be withheld from children in need. In a 2008 editorial, McGowan and Davis recommended that "[u]ntil the risk of neurocognitive injury is understood, pediatric specialties, in conjunction with anesthesiologists and pediatricians, should identify surgical procedures that can be delayed until older ages *without incurring additional risk*"[4] (emphasis in the original). Although it is uncertain what percentage of surgical procedures can be appropriately delayed, their clinical advice remains solid. This same standard should be applied for all procedures on children who require sedation or anesthesia. Pediatricians should be aware of the concerns of the anesthesia community regarding potential neurotoxicity of general anesthetics but also understand the current limitations of the evidence.

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