ANESTHETIC-INDUCED neurotoxicity at the extremes of the life cycle has received considerable attention during the past decade. Although an expanding body of preclinical investigations have unequivocally characterized and confirmed the toxic effect of most anesthetic drugs, neither the qualitative nor the quantitative aspects of the relationship between anesthesia exposure and neurotoxicity have been firmly established in humans. A major limitation of these published clinical reports is the lack of reliable biomarkers allowing rapid noninvasive identification and quantification of toxicity in the central nervous system after anesthesia exposure. In this issue of Anesthesiology, Makaryus et al. present compelling data that could provide some keys to solve these difficulties. The authors used proton magnetic resonance spectroscopy (1HMRS), which provides a noninvasive and quantitative assessment of brain metabolites in vivo both in animals and humans. By using this approach, they show that a 5-h-long sevoflurane anesthesia performed at postnatal day (PND) 7 but not at PND 15 results in a reduction of N-acetylaspartate (NAA) levels, a marker of neuronal maturation, in the thalamus. These developmental stage-dependent effects of sevoflurane on thalamic NAA concentrations are in line with the bulk of previous laboratory observations in rodents demonstrating that anesthetics-induced neuroapoptosis and thereby toxicity are most prevalent at earlier stages of the brain growth spurt.

One important aspect of this work is that it provides us with a proof of concept that repetitive noninvasive imaging of developmental anesthetic neurotoxicity in laboratory animals is feasible. Because 1HMRS has historically demonstrated a correlation between reduced NAA levels and mild cognitive impairment in humans, application of this imaging modality provides a translational link between preclinical and clinical investigations. NAA is the second most abundant molecule in the central nervous system after the amino acid glutamate and produces a prominent 1HMRS signal in the human brain. NAA is primarily expressed in neurons where it is synthesized in the mitochondria from aspartic acid and acetyl-coenzyme A. Given its high concentrations in neurons, NAA, a neuronal osmolyte, is a significant determinant of fluid balance in the central nervous system. In addition, it contributes to energy production in the mitochondria and can also function as a neurotransmitter by acting via metabotropic glutamate receptors. As a neuronal substrate for the production of myelin by oligodendrocytes, NAA is a particularly appealing biomarker to study the effect of general anesthetics on the developing brain because its expression levels constantly increase during the brain growth spurt and reflect neuronal maturation. In addition, both experimental evidence and clinical observations demonstrate decreased levels of this brain metabolite in the context of central nervous system injury. Therefore, the fact that the developmental increase of NAA concentrations is impeded by anesthesia exposure at PND 7 provides an in vivo metabolic correlate of ex vivo biochemical and histologic approaches demonstrating toxicity at this same developmental stage.

Image: R. Makaryus.

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The possibility to noninvasively detect specific biomarkers of anesthesia neurotoxicity can also have a direct influence on clinical research targeting this issue. The authors recently reported a metabolomic comparison of propofol and sevoflurane in children receiving these anesthetics for magnetic resonance imaging (MRI) procedures. They revealed increased lactate and glucose concentrations in the children treated with sevoflurane, which they interpreted as anesthetic-induced catabolic state. They also demonstrated a compelling correlation between increased lactate and glucose levels with postoperative delirium. Measuring brain metabolomics might be of particular relevance when the acute impact of anesthesia in neonates and young children needs to be determined. Indeed, as of today, we do not have any validated biologic marker or psychometric assessment scores in the early postoperative period that could give us information on slight, clinically undetectable neuronal injury. The lack of such tools is an important regrettable issue because even low amounts of neuronal injury in early life can exert long-term impact on central nervous system function. A major drawback of neurocognitive tests is that the assessments are conducted several years after the exposure and may be affected by postexposure experiences, as shown by the role of enrichment environment and activity on attenuation of anesthetic-induced neurocognitive behavior. Thus, assessment of metabolomic profiles immediately after anesthesia/surgery would provide insight into the progression of neurologic injury. Although Makaryus et al. used a powerful 9.4T MRI instrument, quantitative measurement of NAA concentrations can be performed with reliability in basic MRI facilities with a power of 1.3T making the evaluation of this metabolite routinely feasible in the clinical setting. In this context, it is important to note that, in contrast to rat pups that require anesthesia during spectroscopy, such imaging can be done without administering anesthetics in infants using the "feed and wrap" technique. In addition to young patients, magnetic resonance spectroscopy could also be helpful in studying postoperative cognitive dysfunction where reliable biomarkers are also lacking. Currently, 1HMRS is being used to track NAA levels and thalamic neuroconnectivity in premature infants. This is vital link because thalamocortical connectivity is an essential component of functional brain development in infancy.

Do these results and their implications mean that we are on the verge to solve the anesthetic neurotoxicity issue? Although the answer is most probably not, the work of Makaryus et al. gives rise to a whole series of new questions and approaches on this research field. One of the first important issue will be to elucidate whether there is any correlation between changes in anesthetic-induced NAA levels and neurocognitive function. Next, even if such link exists, we will still need to determine whether alterations of NAA concentrations in the perioperative period are directly related to general anesthetics per se or to other factors such as surgery and anesthesia management. Dissecting out such details in humans will be at best very difficult but could be easily performed in laboratory animals, including nonhuman primates. Another intriguing issue will be to ascertain whether the developmental decrease in NAA expression levels, detected shortly after sevoflurane administration, persists over time. Answering this question, especially in humans, is of fundamental importance, because alterations in NAA concentrations may be a harbinger of permanent morphologic reorganization of neurocircuitry. However, it is important to note that even if such lasting morphologic changes do not occur after anesthesia exposure, transient morphologic and functional alterations could still be considered as a plausible cause for long-term cognitive dysfunction. Finally, noninvasive imaging of brain metabolomics after anesthesia exposure would also help us to compare the toxicity profiles of different anesthesia regimens at different ages. The road will be definitely long to obtain answers to all these questions.

Competing Interests
The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

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