Anesthesia and Neurodevelopment in Children

Perhaps the End of the Beginning

David O. Warner, M.D., Yu Shi, M.D., Ph.D., Randall P. Flick, M.D.

EXPOSURE of young animals to most clinically-utilized anesthetics in sufficient doses changes brain structure and affects cognition and behavior in later life. The question of whether these findings can be translated to children has spurred numerous studies, reviews of these studies, and commentaries. In the current issue, two of the leading investigators in this field provide an excellent critical review of the literature about children, including recent studies that have contributed significantly to our understanding.[1] As rightly noted by the review authors, the concerns about whether anesthetics may be "neurotoxic" in children, and indeed the Food and Drug Administration's warning about the potential neurotoxic effects of most anesthetics,[2] were driven primarily by observations in animals, not by an "obvious clinical problem." Concerns about adverse neurodevelopmental outcomes after major neonatal and cardiac surgery are longstanding, but any such effects were typically attributed to the underlying conditions necessitating surgery and other perioperative factors, rather than anesthesia, *per se*. The potential for relatively short-term postoperative changes in behavior is well recognized,[3] but few suspected that anesthesia itself could have long-term neurodevelopmental effects. This lack of suspicion has been used to argue against any significant effects of anesthesia exposure, as surely if this was a real problem, then we would have noticed it by now.[4] Why have we not, other than the possibility that there *is* no problem?

"The potential for adverse neurodevelopmental effects of anesthetics is clearly a complex problem and the answers are not 'obvious'... [and] we grapple with the specific question of whether animal findings translate to children…"

First, there are multiple examples in which concerns about the toxicity of a chemical arose first from laboratory observations, and were then confirmed in children, in the absence of an obvious clinical problem.[5] One particularly tasty example is prenatal exposure to licorice candy. Glycyrrhizin in licorice inhibits a placental enzyme that maintains relatively low fetal levels of glucocorticoids. In animal models, the resulting fetal glucocorticoid overexposure produces, among other things, deficits in learning and memory, as well as increased anxiety behaviors. The potential clinical significance of this observation, first made in animals, was supported in a longitudinal cohort study finding that high licorice consumption in pregnancy is associated with lower intelligence and an increased frequency of attention deficit hyperactivity disorder.[6] Another example is polycyclic aromatic hydrocarbons, a class of environmental contaminants generated by incomplete combustion. Again, initial findings in animal studies were followed by a longitudinal cohort study that measured *in utero* exposure to these compounds and confirmed a strong association between exposure and multiple neurodevelopmental problems.[7] Imaging studies identified specific alterations in brain structures that mediated these effects, providing strong evidence of a causal link. These and other examples have several implications, including: (1) causal inferences can be made from animal and observational human studies in the absence of randomized clinical trials; (2) the power (and perhaps, necessity) of longitudinal cohort studies; and (3) whether the initial observations are made in the laboratory or in clinical practice is not germane to the validity and significance of the finding.

Another reason that the problem may not be "obvious" is because injury may require time to be made manifest. Higher cognitive skills and complex behaviors may require considerable time to develop (as any piano teacher can tell you), and the consequences of injury early in development

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Accepted for publication December 13, 2017. From the Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, Minnesota.

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may not be apparent until later in life, far after a childhood anesthetic has receded into memory.[8] Delayed emergence of symptoms also provides the opportunities for mitigating influences, such as the effects of environmental enrichment noted in some animal studies,[9] which may obscure evidence of effects.

Third, if only a small number of children are at risk, it may be difficult to observe effects by examining mean differences derived from a population sample. To take an oversimplified example, if an environmental exposure causes a relatively large effect in a relatively small number of susceptible children (say a 10% decrease in intelligence in 10% of the children), the effect on the intelligence of the overall population is only a 1% decrease—yet is very relevant to the 10% of children affected. The observation that several of the studies reviewed find an increased risk of having very poor performance, or not being able to complete the outcome assessment, hints at such a possibility. Analytic techniques, such as moderator and cluster analyses, are available to query for such possibilities, but have seldom been employed.

Finally, because no one thought it possible that anesthesia exposure could cause significant long-term problems, no one looked for a problem. As the review authors note, it is hard to know even what to look for. It may be also hard to determine what is "significant." Modeling suggests that even if a factor such as an environmental exposure causes quite modest impairment in outcomes such as intelligence, it can have a significant population-level impact if the factor is prevalent in the population.[10] However, are modest declines in intelligence or teacher-assessed readiness for school significant to *individual* families?[11,12] Some studies find that multiple exposures to anesthesia are associated with a doubling of the risk of behavioral and learning difficulties[13]—yet even so, the majority of exposed children do not have such difficulties. Is this significant? Who decides? The physician? The parents? The children? Although the concept of patient (or family)-centered outcomes has gained currency as a tool to evaluate the real-world impact of medical practices, this concept has not been prominent in discussions of anesthesia neurotoxicity. Have we ever really talked with parents or children about what is important to them about their perioperative experiences? About whether they noticed any long-term consequences of procedures requiring anesthesia? Should we?

As we grapple with the specific question of whether animal findings translate to children, it forces us to deal with the more general question of the long-term consequences of procedures requiring anesthesia. Regardless of whether anesthesia in sufficient doses causes neural injury, multiple other aspects of the perioperative experience could also affect child health and well-being. For example, stressors of various kinds, such as minor or major life events (including medical events), can have both short- and long-term consequences to child health and well-being. With the exception of studies looking at relatively short-term behavioral changes after surgery, we have little idea of how most procedures affect child and family well-being, nor have we considered the potential impact of the many factors that determine these important outcomes.

Integrating the potential effects of the multiple factors that could affect outcome is a challenge, but one that is common in studies of neurodevelopment. Conceptual frameworks are useful tools to address this challenge, postulating how these factors and outcomes are related, and serving as a roadmap to investigate these relationships. We propose a potential framework that might be useful to guide studies of

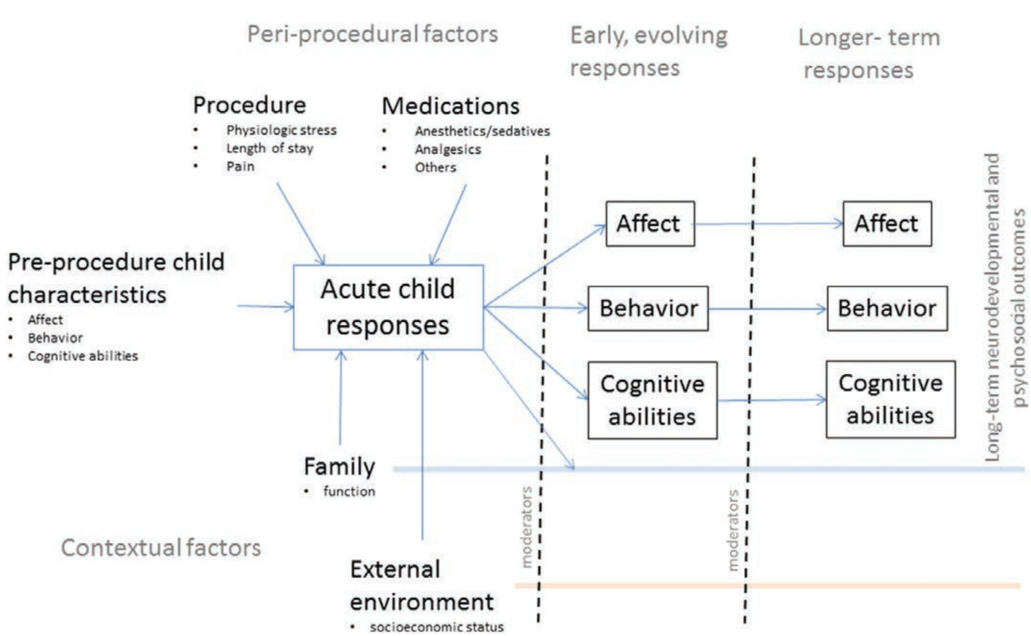

Fig. 1. Example of a conceptual framework describing potential factors that affect outcomes after procedures requiring anesthesia. Periprocedural and contextual factors interact to determine acute child responses to the procedure; early and longer-term responses in affect, behavior, and cognitive abilities continue to be moderated by these contextual factors as they evolve.

how procedures requiring anesthesia affect outcomes, building on existing models of pediatric medical trauma stress (fig. 1).[14] In this framework, a child's baseline characteristics, procedural factors (including physiologic responses to surgical trauma), and medications (including anesthetics) contribute to a child's acute responses to the general anesthesia encounter. The acute responses may lead to early, evolving changes in affect (*e.g.*, anxiety), behavior, or cognition. Changes in the early postoperative period may resolve or evolve into longer-term consequences for child development. Contextual factors, including family function, may moderate both a child's acute response to anesthesia and the evolution of short- and longer-term outcomes. In turn, the periprocedural experience itself may also modify these contextual factors (*e.g.*, the impact of chronic childhood diseases on family functioning is well documented[15]), which can further influence subsequent outcomes.

Evaluation of such a framework requires careful assessment of each factor, which typically requires longitudinal cohort studies that can prospectively determine which factors should be assessed, rather than relying on what data happen to be available. These studies are both difficult and expensive, requiring meticulous design and extensive follow-up. The failure of the National Children's Study serves as a cautionary tale of an overly-ambitious longitudinal child health study.[16] However, there are numerous other examples (such as those previously mentioned) of how prospective cohort studies provided critical insights into how factors, such as exposures to toxins, affect important patient-centered outcomes.[5] We suggest that it is time for a comprehensive longitudinal cohort study of periprocedural child health, grounded in a conceptual framework. It should not be restricted to the narrower question of whether neurotoxic effects of anesthesia in animals translate to humans, but rather should investigate which factors determine patient- and family-centered outcomes after pediatric procedures requiring anesthesia, so that we can intervene on those amenable to modification. Such an effort would also have the desirable side effect of demonstrating our commitment as perioperative physicians who care about more than just getting children safely through the immediate perioperative period, but rather the long-term well-being of the little ones we serve.

The potential for adverse neurodevelopmental effects of anesthetics is clearly a complex problem and the answers are not "obvious." Complex problems require time, patience, and careful thought to address, and this area is no exception. The timely review of Davidson and Sun shows that although much has been accomplished, this field of investigation is still relatively young, and we should not be discouraged that the question has not yet been fully answered, especially for prolonged or multiple anesthetics. Appropriating a quote from Winston Churchill, we are certainly not at the end [of our study of how anesthesia exposure may affect the developing brain,] but we may be at the end of the beginning. Taking a wider view of how procedures may affect child health and well-being, and generating the requisite data, may not only help answer the specific translational question regarding anesthesia neurotoxicity observed in animals, but may provide actionable insights into the many other factors that could determine outcome after procedures requiring general anesthesia in children.

Competing Interests

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Correspondence

Address correspondence to Dr. Warner: warner.david@mayo.edu

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