Chapter 3

Anesthetic Neurotoxicity in Children

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A nine-month-old, 7 kg male arrived for primary repair of hypospadias. He was born at 32 weeks and required ligation of a patent ductus arteriosus at 35 weeks of age via a thoracotomy. At three months, he underwent a brain MRI after a seizure, with no critical findings. During the routine pre-operative evaluation, the parents ask about the possible harmful effects of anesthesia on their child and are concerned because this is his third exposure to general anesthesia.

How Many Children Undergo Procedures with Anesthesia Annually?

In the United States, about 1.5–2 million infants under one year of age undergo anesthesia each year for a variety of surgical procedures or diagnostic tests.

What Is the 2017 Concern/Warning About General Anesthesia from the Food and Drug Administration?

In 2016, with a revision in 2017, the US Food and Drug Administration (FDA) issued a warning regarding the administration of anesthetics in children. Specifically, the warning states:

> The U.S. Food and Drug Administration (FDA) is 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.

What Studies Led to the FDA-Issued Warning?

The initial studies concerning for neurotoxic effects of anesthetics in young children date back to 1999. Ikonomidou et al. (1999) demonstrated that administration of dizocilpine (a ketamine analog) in pregnant rats and rat pups resulted in significant neuronal cell death compared to unexposed controls.

Following this study, other groups were able to demonstrate similar neurotoxic effects using halogenated agents as well as propofol in rat and rhesus macaque brains for both neonatal and fetal animal groups.

Based on the Animal Studies, Are the Effects of Neural Toxicity Dose Dependent?

Early studies using ketamine by Ikonomidou et al. (1999) demonstrated a significant dose-dependent effect on neuroapoptosis.

Summarize the Human Studies Evaluating Neurologic Effects of Anesthetics in Children

Several studies have been presented evaluating the long-term effects of early anesthesia exposure on neurological development.

An early study by Flick et al. (2011) compared 350 children with anesthesia exposures before age two. These patients were compared with 700 propensity-matched controls evaluating for the incidence of learning disabilities and school specialized educational programs. They concluded that repeated (not a single) exposure to anesthesia prior to age two was associated with a risk for development of learning disabilities.

In 2016, Sun et al. published the Pediatric Anesthesia Neurodevelopment Assessment (PANDA) study which reported the findings of a longitudinal sibling-matched multicenter study.

They compared unexposed siblings to siblings exposed to a single anesthetic for inguinal hernia repair prior to age two. The patients underwent

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neuropsychological testing for IQ and neurocognitive functions at a mean age of ten years. They concluded that a single exposure to anesthesia prior to thirty-six months in age did not result in any statistically significant differences in IQ scores in childhood.

In 2016, Davidson et al. presented the findings of the General Anesthesia compared to Spinal anesthesia (GAS) trial. This multi-institutional, prospective, randomized-controlled equivalent trial compared Bayley Scales of Infant and Toddler Development III, assessed at two years in children undergoing inguinal hernia repair younger than sixty weeks post-conceptual age. Patients were randomly assigned to either awake-regional anesthesia (spinal) or sevoflurane-based general anesthesia. They found no difference in Bayley III scores in children having one hour or less of anesthesia compared with unexposed children (regional group). The primary outcome of the study released in 2019 concluded that less than 1 h of general anaesthesia in early infancy did not alter neurodevelopmental outcomes at five years of age compared with awake-regional anaesthesia

Table 3.1 What drugs are included in the 2017 concern/warning from the US Food and Drug Administration (FDA)?

• Desflurane	• Propofol	• Ketamine
• Halothane	• Pentobarbital	• Etomidate
• Sevoflurane	• Midazolam	• Methohexital
• Isoflurane	• Lorazepam	

What Future Studies Are Occurring?

For each of the landmark studies, questions exist on the extrapolatability from animal models, use of behavioral and IQ testing as surrogates for neuroapoptosis, and the generalizability of the populations studied. Other concerns include the translatability of neurodevelopmental phases from the animals studied to humans, and the medication doses and duration of exposure.

However, conducting these studies in humans is unethical, which requires us to rely on these extrapolations.

In addition to reporting the primary outcome of the GAS trial, the Toxicity of Remifentanil – Dexmedetomidine (T-REX) study is expected to evaluate the use of dexmedetomidine and remifentanil on children undergoing anesthesia. (See https://clinicaltrials.gov/ct2/show/NCT02353182.)

What Can You Tell Parents About Neuroapoptosis?

Parents of young children should be made aware of the risks of anesthesia on the developing brain as suggested by the FDA warning. At Texas Children's

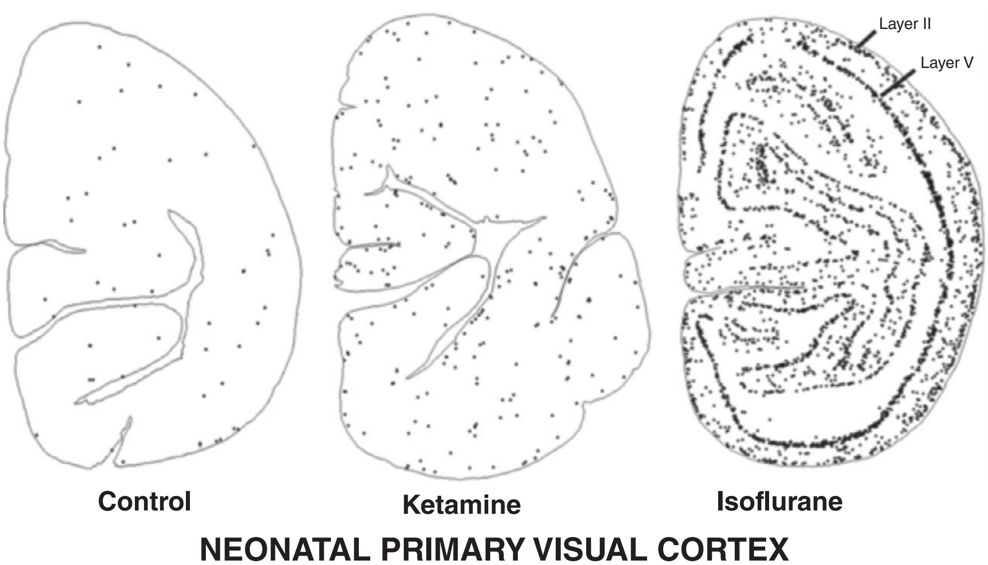

Figure 3.1 Pictorial demonstrating the degrees of neuroapoptosis seen in rhesus macaque brains in control subjects contrasted with those exposed to ketamine and isoflurane. Reproduced with permission of Wolters Kluwer Health, Inc. from Brambrink AM, et al. *Anesthesiology* 2012;116:372–384.

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Hospital, in children with potentially deferrable procedures and those predicted to undergo multiple anesthetics in early childhood, the FDA warning is discussed with parents and documented. Discussion and documentation should be performed according to hospital and state guidelines.

Items to discuss with parents include:

- Human studies suggest that a short and single exposure to anesthesia appears to be safe.
- There is evidence that prolonged (>3 hours) or repeated exposures could have negative effects on behavior or learning.
- More research, especially in children, is needed to truly understand the effects of anesthesia.

We encourage parents to ask their providers:

- How long is the surgery or procedure expected to take?
- Is the procedure potentially deferrable to a later date?
- Are additional procedures likely to be needed?

What Can I Do to Limit Anesthetic Exposure in Young Children?

When evaluating children for anesthesia and surgery, it is important to identify young children scheduled for potentially deferrable procedures, and certainly procedures that are expected to exceed three hours. This is crucial in children who are likely to undergo multiple anesthetics in early childhood. Thankfully, most children do not fall into this category. However, the child presented in this chapter's case example is one in which multiple anesthetics were performed in infancy with a planned hypospadias revision that may be deferrable until later in childhood.

- When possible, perform regional anesthetic techniques.
- Minimize use of inhalation agent to reduce total exposure.
- Use opioids and dexmedetomidine to reduce the exposure to halogenated agents.

Suggested Reading

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