

Early Exposure to Anesthesia Linked to Learning Disabilities

Deborah Brauser

October 4, 2011 Repeated exposure to anesthesia for early-life surgeries may lead to neurodevelopmental problems in children, new research suggests.

A large cohort study showed that children who underwent 2 or more anesthetic/surgery episodes before the age of 2 years had a nearly 2-fold increased risk for developing learning disabilities (LDs) by their late teens compared with their counterparts who had not received anesthesia.

Receiving multiple early-age exposures was also significantly associated with the need for school-based individualized educational programs (IEPs) related to speech and language impairment and for lower scores on tests of cognitive ability and academic achievement.

"We found these results, including an almost 2-fold increase in [LDs], after controlling for comorbidity," lead author Randall Flick, MD, MPH, associate professor of anesthesiology and pediatrics at Mayo Clinic, Rochester, Minnesota, told *Medscape Medical News*.



Dr. Randall Flick

"It's important to reassure parents that single exposures to anesthesia don't seem to be associated with a problem and that the need for repeated surgeries among young children is relatively unusual," added Dr. Flick.

"This is likely to affect a relatively small number of children. Nonetheless, it's quite concerning."

The study [was published online](#) October 3 in *Pediatrics*.

Controlled for Comorbidity

According to the researchers, studies of young animals have shown that most anesthetic drugs can cause neurodegeneration. However, previous research examining the link between anesthetics/surgery and cognition in human children "have been few, have relied on single outcome measures, and have not controlled for comorbidity."

A population-based, matched cohort study, [first published](#) by the Mayo Clinic investigators in 2001, included 8548 children born in Rochester, Minnesota, between January 1976 and December 1982.

[As reported](#) in 2009 by *Medscape Medical News*, the investigators examined the link between anesthesia exposure and LDs in some of these participants. However, Dr. Flick said that a criticism of that study was that it did not control for health status.

"After it was published, some people said that the problem we were measuring was not anesthesia exposure but comorbidity. In other words, the kids who required multiple surgeries were not healthy. And because they were not healthy, then they had [LDs]. So the US Food and Drug Administration [FDA] asked us to do a study that would control for the effects of comorbidity."

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For the analysis, the investigators evaluated data on 350 of the participants who were exposed to anesthesia before the age of 2 years (68% male) and then age-matched each of these "cases" to 2 healthy controls who were not exposed (n = 700, 68% male).

The controls were also matched according to "factors known to influence the incidence of LDs," including sex, mother's education, birthweight, and gestational age.

Health status was determined through the use of the American Society of Anesthesiologists Physical Status and the Johns Hopkins adjusted clinical groups Case-Mix System.

No Risk From Single Exposure

All children underwent the group-administered Test of Cognitive Skills and California Achievement Test, as well as the individually administered Wechsler Intelligence Scale for Children and Woodcock-Johnson Battery test for academic achievement through their schools.

Study outcome measures included the need for an IEP for emotion/behavior (such as anxiety, depression, unusual behavior patterns, aggression, and impulsivity), LDs before the age of 19 years (in reading, written language, and/or mathematics), and achievement and cognition scores.

Results showed that 286 of the children exposed to general anesthesia before surgery by the age of 2 years received it only once, whereas 64 were exposed more than once.

The median duration of anesthetic exposure was 75 minutes, and combinations using halothane (87.5%) or nitrous oxide (88.1%) were the most frequently used anesthetic medications.

Of the children exposed to anesthesia/surgery just once, 23.6% developed LDs by the age of 19 years vs 21.3% of the unexposed participants. However, 36.6% of those with multiple exposures developed LDs.

After adjustment for health status, this translated into a significantly increased risk for LDs in those with the multiple exposures (hazard ratio [HR], 2.12; 95% confidence interval [CI], 1.26 - 3.54), but not for those with just 1 exposure.

"The size of the study was not sufficient to differentiate what specific type of [LD] may occur. There's a good deal of overlap; kids who have 1 type often have another type as well," explained Dr. Flick.

Although exposure was not a significant factor in children receiving an IEP for emotion/behavior, multiple exposures were found to be a significant risk factor for the need for an IEP for speech/language (HR, 4.76; 95% CI, 2.48 - 9.12).

Lasting Consequences?

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"Not surprisingly, after we adjusted for comorbidities, the results from this study are almost exactly the same as those found in the study we published in 2009," added Dr. Flick.

He reported that the FDA recently convened its advisory committee, on which he sits, to examine whether they should release a direct communication advising clinicians and parents on this topic.

"The committee said 'no, we don't have enough information to be able to provide good guidance to families about this problem.' And that's because there's so much variation. So it was our view that individual families should be advised by their physician, based on the risks and benefits for their child, on when the best time for a specific procedure might be," he said.

"In addition to all the other factors that go into determining the balance of risk and benefits for any procedure, this is simply 1 more factor in that calculus."

The minutes from the advisory committee's meeting on this issue are available on the [FDA Web site](#).

Hot-Button Issue

"The clinical significance of anesthetic neurotoxicity is controversial and under heated debate," writes Robert K. Williams, MD, from the Department of Anesthesia and Pediatrics, College of Medicine at the University of Vermont in Burlington, in an accompanying editorial.

"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, Dr. Williams writes that the new study by Dr. Flick and colleagues focuses on a "disquieting notion" that cognitive or behavioral deficits may develop in otherwise healthy children after receipt of general anesthesia.

Although these results "are provocative," he notes that several limitations are associated with its retrospective epidemiologic approach. He adds that pediatricians will have to examine whether the benefits outweigh "the purported but completely unquantifiable risk" from anesthesia.

"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," writes Dr. Williams.

"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."

Because regional anesthesia seems to be free of risk from neurotoxicity, this option should be explored in appropriate cases. However, most surgical procedures will require general anesthesia, and neither surgery nor anesthesia should be withheld from children in need.

However, more research and guidelines are needed about this issue. To that end, a public-private partnership [has been formed](#) between the FDA and the International Anesthesia Research Society, "and several prospective human trials are underway," Dr. Williams reports.

While waiting for definitive answers, he suggests that pediatricians should prepare themselves for questions and requests for alternatives from anxious parents.

"Because regional anesthesia seems to be free of risk from neurotoxicity, this option should be exploredâ€¦in appropriate cases. However, most surgical procedures will require general anesthesia, and neither surgery nor anesthesia should be withheld from children in need," he writes.

"Pediatricians should be aware of the concernsâ€¦but also understand the current limitations of the evidence."

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