Deficits Seen After Single Childhood Anesthesia Exposure

Nancy A. Melville

August 28, 2012 — Children exposed to anesthesia before the age of 3 demonstrate signs of long-term language and reasoning deficits at age 10, even when the exposure occurs only on a single occasion, a new study suggests.

A research team led by Caleb Ing, MD, of Columbia University's College of Physicians and Surgeons, evaluated data on 2608 children in the Western Australian Pregnancy Cohort (Raine) Study who were born between 1989 and 1992. Among these children, 321 had been exposed to anesthesia before the age of 3, and 2287 were unexposed.

Neuropsychological assessments at age 10 indicated that children who had been exposed to anesthesia showed significant deficits in receptive and expressive language, as well as abstract reasoning, compared with children in the nonexposed group.

Contrary to previous studies, which have shown cognitive deficits only in relation to 2 or more anesthesia exposures, the new study showed long-term impairment even with a single exposure.

"These results were unexpected since prior studies had not documented deficits with single exposures," Dr. Ing told Medscape Medical News.

This study was published online August 20 and will appear in the September issue of Pediatrics.

Direct Assessment

A key reason why the single exposure association emerged in the new study could be the availability of data reflecting directly administered neuropsychological assessments, whereas previous studies used outcomes such as parent and teacher surveys, academic scores, and standardized test results, the authors suggest.

"Our study used outcomes that may be more sensitive than those used in prior studies, which could be why we were able to detect a difference," Dr. Ing said.

The Australian cohort, for instance, had gathered data on scores on the directly administered Colored Progressive Matrices (CPM) neurological test. Those tests showed that, compared with children who had had no exposure to anesthesia, exposed children achieved lower cognitive scores.

Children exposed to anesthetic also had lower receptive and expressive scores on the Clinical Evaluation of Language Fundamentals tests (Receptive [CELF-R] and Expressive [CELF-E]).

After adjustment for demographic characteristics, increased risk for disability in the anesthesia-exposed group continued to be evident in scores related to language and cognition.

Risk for Disability in Language and Cognition With Anesthesia vs No Anesthesia

TestAdjusted Risk Ratio95% Confidence Interval

CELF-R1.871.20 - 2.93

CELF-E1.721.12 - 2.64

CPM1.691.13 - 2.53

CELF-R, Clinical Evaluation of Language Fundamentals test–Receptive; CELF-E, Clinical Evaluation of Language Fundamentals test—Expressive; CPM, Colored Progressive Matrices test.

It is important to note that increased risk for language and cognition deficits remained after adjustment for children with a single exposure to anesthesia.

Risk for Disability in Language and Cognition With a Single Anesthesia Exposure

TestAdjusted Risk Ratio95% Confidence Interval

CELF-R2.411.40 - 4.17

CPM1.731.04 - 2.88

No differences based on anesthesia exposure status were observed between any of the groups in terms of behavior, visual tracking and attention, or fine and gross motor function.

"Our findings show that not all cognitive domains are uniformly affected," the authors write.

Various factors could explain why deficits were seen in some areas of cognition but not others, Dr. Ing noted.

"It's possible that these specific domains may be more vulnerable, or that those neuropsychological assessments are more sensitive," he speculated. "These results, however, are important as they will help guide future studies."

The neurotoxic effects of anesthetic exposure on developing brains have been well documented in animal studies, and those studies have helped to shed light on some of the possible mechanisms at play, Dr. Ing explained.

"In animal studies, the hypotheses have been that there is depression of signaling in the brain, resulting in the death of some neurons, as well as interference with the creation of neuronal networks in the brain while it is developing. It is unknown if this occurs in humans."

The type of anesthetic believed to have been used in most cases in the study was halothane. Although halothane is no longer available in the United States, this anesthetic has been shown in animal studies to have neurotoxic effects similar to those of other anesthetics, hence similar findings could be expected with other agents, the authors noted.

Despite findings in animal studies, the surgical procedures themselves and the conditions behind the need for surgery are commonly seen as important potential confounders when studies show deficits related to anesthesia exposure.

The authors noted that the fact that the "vast majority" of patients in the cohort underwent minor procedures "leads us to believe that significant comorbidity is unlikely to confound our results."

Potential Confounders

Mark Singleton, MD, who serves as chair of the American Society of Anesthesiologists (ASA) Committee on Pediatric Anesthesia, said he believes that the role of the potential confounders is difficult to ignore. Dr. Singleton was not involved in the study.

"Some of the surgeries were very significant, such as heart surgeries or craniotomies, and I think it's a little dangerous for us to conclude that what we're looking at are outcomes related to anesthesia exposure, because we just don't know that to be certain," said Dr. Singleton, who is an adjunct professor of anesthesiology at Stanford University, in Palo Alto, and practices in San Jose, in California.

"The learning disabilities could be associated with surgery, with whatever disease process led to the surgery, or [with] some diagnostic procedure."

"In addition, there are a myriad of complex psychosocial effects on children requiring surgery early in life," he added. "It can affect the entire family dynamic, so these are caveats that need to be at the front of everyone's mind as we discuss this."

The US Food and Drug Administration (FDA) convened a meeting of experts in 2011 to address issues raised about the safety of anesthesia exposure in children; however, no conclusions were reached on actions to take, largely because of the lack of research on humans.

In response to concerns, the FDA joined with the International Anesthesia Research Society to form a multiyear collaboration called SmartTots to improve the safety of anesthetic agents for children.

Although no clinical guidelines have come out of the partnership, Dr. Singleton said that concerns regarding anesthesia safety are prominent on the radar of pediatricians.

In every possible case, there should be a real consideration about postponing surgery and anesthesia until the child is older…

"I think one of the reasons this article was published in Pediatrics is to heighten awareness among pediatricians and let them know that there are unanswered questions with anesthesia, and a trip to the operating room should not be made lightly," he said.

"In every possible case, there should be a real consideration about postponing surgery and anesthesia until the child is older."

Dr. Ing echoed the sentiment, while underscoring that the study's findings should not raise doubt about the importance of surgery — and anesthesia — when necessary.

"I want to emphasize that our results do not mean that children should not have surgery if it is needed," he said. "Parents should consult with their surgeon and pediatrician to see if the procedure is necessary at this time, and if anesthesia is needed for that procedure."

"If the surgery is needed, they should not delay and should proceed with the surgery and anesthesia. However, if it is determined that a procedure is completely elective and there are no risks for delay, postponing the procedure could be a reasonable choice."

The authors and Dr. Singleton have disclosed no relevant financial relationships.

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From below: Neuropsychological assessments at age 10 indicated that children who had been exposed to anesthesia showed significant deficits in receptive and expressive language, as well as abstract reasoning, compared with children in the nonexposed group.