Can We Really Suggest that Anesthesia Might Cause Attention-deficit/Hyperactivity Disorder?

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THE impact of anesthesia on the developing brain continues to be hotly debated. In this issue, Hu *et al.*,[1] from the Mayo Clinic, Rochester, Minnesota, report an association between childhood exposure to multiple anesthetics and increased risk of learning disability and attention-deficit/hyperactivity disorder (ADHD). The study uses a well-established birth cohort and is similar to two studies published previously by the same Mayo Clinic group.[2,3] The earlier studies were criticized for including children who were anesthetized in an era that relied on somewhat outdated drugs and monitoring. The study reported in this issue included children anesthetized with more contemporary agents and monitoring. The results are almost identical to the previous studies. All find an association between exposure to anesthesia in early childhood and subsequent diagnosis of learning disability and/or ADHD, and the associations were stronger with multiple exposures compared with single exposures.

"…given our understanding of the causes of [attention-deficit/hyperactivity disorder], and the extent of and nature of injury seen with anesthesia exposure, the added risk is likely to be very small…"

When determining whether an association is causal, several factors are important. First can the findings be replicated in different populations? There are now several cohort studies that have examined the association between anesthesia and a range of neurodevelopmental outcomes.[4] The results are mixed. Some large, population-based cohort studies have found evidence for weak association between exposure to anesthesia in early childhood and slightly poorer performance in school grades or tests of school readiness in preschoolers. Others have not found this association. Similarly, some cohort studies have found evidence for an association between exposure to anesthesia in early childhood and deficits in psychometric tests of memory and cognition, whereas some other cohort studies and one trial have not found any evidence for such an association.

The second consideration in interpreting these findings is the issue of confounding variables. As the authors point out, the association may be entirely due to confounding. In other words, children who have anesthesia may have underlying medical, neurologic, or developmental problems that increase their risk of ADHD, and thus an association may be found between anesthesia and ADHD, although the anesthetic itself does not cause the ADHD. The authors try to reduce confounding by using propensity matching, but this technique cannot completely remove the possibility of confounding. Although Hu *et al.*[1] adjusted for sex, birth weight, gestational age, mother's education, and socioeconomic status, they did not adjust for the key confounder of underlying condition. Sicker children get anesthetics, and sicker children have more developmental issues. Other perioperative factors apart from any direct anesthetic toxicity may also confound the results.

The ability of the Mayo Clinic group to replicate their findings may reinforce the evidence that having anesthesia is associated with ADHD, but it does not necessarily reduce the chance that the association is due to confounding. The

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same confounding factors may still be present. It is, however, important to note that the association remains, although there is presumably better perioperative care and monitoring in the more recent cohort. This may be seen as some evidence that the association between anesthesia and ADHD is not due to factors that relate to monitoring or other aspects of perioperative care that have improved over the last decade.

The third element in determining the likelihood of a causal relationship is biologic plausibility. To fully interpret the article by Hu *et al.*,[1] readers need an understanding of the pathogenic mechanisms causing ADHD.

What do we know about the cause of ADHD? ADHD has a childhood prevalence of approximately 5%, with no evidence of an increase internationally over the past 30 yr[5] (the incidence in the study by Hu *et al.*[1] was much higher). The ADHD and learning disability phenotypes, like those of all developmental and psychiatric disorders, are the end result of complex causal sequence pathways involving interactions between a wide range of genetic and environmental risk and protective factors, each individually of small effect.[6] The symptoms of ADHD are underpinned by disordered biochemical function of the attentional network, involving multiple brain structures including the prefrontal cortex, deep grey matter, limbic system, and cerebellum. Family, twin, and adoption studies conducted over the past 20 yr have demonstrated that ADHD is strongly genetic. Genetic risk factors include polymorphisms in genes involved in catecholamine activity, such as those coding for dopamine receptors and transporters (*e.g.*, dopamine receptor-D4 and dopamine active transporter-1). Chromosomal microarray studies have shown that populations with ADHD carry a mean 2.1-fold increased burden of copy number variants compared with control subjects. These genetic differences contribute to cumulative vulnerability (traits), and some research groups are developing polygenic risk scores to estimate overall pathogenic load for ADHD and other developmental disorders. Individuals with a similar risk burden (*e.g.*, full biologic siblings) may present with other developmental or mental health disorders, such as intellectual disability, autism spectrum disorder, or mood disorders, a concept in developmental psychopathology known as "multifinality." This phenomenon suggests that these disorders share common defects in molecular mechanisms and cellular processes, such as aberrations in neural communication and synaptic plasticity.[7]

Environmental factors that may contribute to the risk of ADHD include exposure to embryopathic neurotoxins, such as alcohol, or childhood neurotoxins, such as lead, severe early life psychosocial deprivation, harsh and coercive parenting, and in some cases dietary sensitivities.[8] Again, these risks are not specific to ADHD; rather, the exposures contribute to the general risk of developmental pathology across clinical syndromes. The executive cognitive functions (*e.g.*, working memory, task planning, sustained attention, and inhibitory control) are phylogenetically the most recently evolved human capacities, and therefore particularly vulnerable to loss after central nervous system insult. Thus, learning and behavioral difficulties are not uncommonly seen as sequelae of major cerebral insults, such as hypoxic–ischemic injury, severe encephalitic illnesses (*e.g.*, postencephalitic behavior disorder in the Spanish flu pandemic of the 1920s), traumatic brain injury, uncontrolled raised intracranial pressure, or central nervous system irradiation. In summary, cerebral injury caused by a toxin or similar insult can increase the risk of developing ADHD and learning disability in some genetically susceptible children. However, due to the multifactorial nature of the condition, the impact is likely to be very small at a population level. It is, however, still unknown whether the toxicity seen with anesthesia in animal models is sufficient to have this effect, particularly if the exposure is relatively brief.

Another approach to examining biologic plausibility is to consider whether the neurobiologic differences reported in ADHD are consistent with the preclinical data seen with anesthesia exposure. ADHD is thought to result from dysregulated modulation of neural plasticity. Structural magnetic resonance imaging studies consistently show reductions in cortical thickness, total cerebral volume, and volume of a number of subcortical structures.[9] Additionally, diffusion tensor imaging reveal reduced white matter connectivity between the frontal cortex and other brain structures.[10] Human resting state functional magnetic resonance imaging investigations revealed altered connectivity patterns in multiple neuronal systems in ADHD patients compared with control subjects.[10] How do these findings compare with the morphologic changes seen in animal models after exposure to anesthetics? There is strong experimental evidence that early life anesthesia exposure can lastingly impair synaptogenesis and neural network formation[11] and some limited morphologic data showing lasting brain structural anomalies in children exposed to anesthesia/surgery.[12] In summary, there are some similarities in the morphologic changes. The study by Hu *et al.*[1] provides some impetus for additional preclinical studies to determine whether the preclinical changes seen with anesthesia are indeed consistent with changes that we would expect to see with ADHD.

Suggesting that anesthesia might cause ADHD or a learning disability is a big step, which may generate substantial public concern. From what we know of the causes of ADHD, it is biologically plausible that anesthetic exposure may contribute to ADHD. However, given our understanding of the causes of ADHD and the extent of and nature of injury seen with anesthesia exposure, the added risk is likely to be very small, possibly far smaller than the likely impact of the confounding factors seen in the study by Hu *et al.*[1] Numerous other environmental factors have been suggested to possibly cause ADHD (*e.g.*, food additives, adverse parenting practices, and electronic media exposure). The evidence for most of them is weak; the evidence that anesthesia causes ADHD also remains weak.

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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