

# Developing brain and general anesthesia – is there a cause for concern?

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## Abstract

Skilled management of sick premature babies and very young children has resulted in numerous exposures of their brains to a variety of anesthetic agents designed to achieve the substantial depth of neuronal inhibition required for complete loss of consciousness and insensitivity to pain. Unfortunately, our recent animal findings suggest that commonly used general anesthetics are damaging to developing neurons and cause significant neuronal deletion in vulnerable brain regions. In addition, emerging animal and human data suggest an association between early exposure to general anesthesia and long-term impairment of cognitive development. Consequently, the prudence of frequent anesthesia exposure of this population is now being scrutinized. It is important to note that on the basis of currently available information, there are still considerable differences of opinion regarding the clinical relevance of the animal findings. Since there is insufficient evidence establishing a clear association between animal and human findings, it would be premature to suggest major changes in current clinical practice.

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## Introduction and context

The exposure of very young children to general anesthesia is becoming a common occurrence. The frequency of operating suite visits has increased, as have the lengths of stay in intensive care units, resulting in the annual administration of more than 3 million general anesthetics to the pediatric patient population [1].

These practices generally have been considered to be safe since there were no reports indicating otherwise. Now our work and that of others have shown that clinically used general anesthetics are potentially damaging to the developing mammalian brain. When used at the peak of brain growth, which coincides with synaptogenesis, they cause widespread neurodegeneration in vulnerable brain regions in mammalian species [2-7]. It appears that anesthesia-induced neuronal damage is apoptotic and involves several pathways of caspase activation, ultimately resulting in massive DNA fragmentation [2,7-9]. Both the intrinsic, or mitochondria-dependent apoptotic pathway

and the extrinsic, death receptor-dependent pathway get activated by general anesthesia [7,8]. In addition, general anesthesia was shown to cause disturbances in the homeostasis of the neurotrophic factors (brain-derived neurotrophic factor, in particular) [9]. Thus, it appears that general anesthesia causes highly complex disturbances in neuronal signaling and communication at an early stage of neuronal development and that the timing of anesthesia exposure during brain development is crucial in determining the severity of anesthesia-induced neurotoxicity; that is, the immature brain is most sensitive at the peak of its development [4,7].

## Recent advances

Although there is no doubt that general anesthesia causes significant patho-histological damage to the developing animal brain, the crucial question of whether the exposure to general anesthesia has any lasting functional effects in humans and animals was posed. Extensive behavioral studies of rats and mice indicate that

exposure to general anesthesia at the peak of synaptogenesis does indeed cause learning and memory deficiencies, alters spontaneous behavior, and causes a lack of habituation later in life [2,10,11]. Interestingly, the gap in learning abilities between control and anesthesia-treated animals progressively widens during adulthood [2].

These preclinical studies, which clearly implicate anesthetic agents in a variety of behavioral disturbances indicative of impaired neurocognitive development, provided the major impetus for methodical investigations into the possibility of anesthesia-induced neurotoxicity in very young children. Although such investigations are still at an early stage, the clinical evidence that has emerged over the last couple of years has begun to point to potentially detrimental effects of anesthetic agents *per se* on behavioral development. These retrospective human studies challenge the assumption that the emotional shocks of hospitalization and separation from family and the physical trauma of surgical intervention were the main factors in children's regressive behavioral changes known for years to occur postoperatively. Because the postoperative psychological disturbances observed in children under 2 years of age are presumed to be due, in part, to separation from family members, it has generally (and ironically) been thought that it is best to perform surgical procedures immediately after infants are born, before bonding with family members has occurred and before the infants have become emotionally attached to the outside human world. Unfortunately, this is the time when the brain is perhaps most vulnerable to anesthesia-induced neurotoxicity.

Several early studies reported that, on average, the incidence of surgery-associated psychological disturbances and new behavioral disturbances in children ranged from 9% to 20% and suggested that children under 2 years of age were at increased risk despite the variety of different anesthetic agents that were used [12-15]. The first report to suggest a possible relationship between anesthesia and long-term impairment of cognitive development was by Backman and Kopf [16]. Although the surgical procedure (removal of congenital nevocytic nevi) was minor, the authors reported an increased incidence of cognitive impairments compared with preoperative baseline which were described as regressive behavioral changes lasting up to 18 months after general anesthesia. Again, children younger than 3 years were the most sensitive. A few of the very recent studies seem to concur with these earlier observations. For example, a population-based, retrospective, birth cohort study (n = 5357 children) by

Wilder *et al.* [17] showed that although a single exposure to general anesthesia was not associated with a greater risk of learning disabilities than that among a no-exposure group, children who received two or more general anesthetics were at significantly increased risk for learning disabilities. Moreover, that risk increased with longer cumulative duration of anesthesia exposure. In support of the finding that duration of anesthesia is potentially an important consideration is a more recent study from this group of investigators which shows that brief exposure to general anesthesia at the time of cesarean birth had no effect on cognitive development later in life [18]. Interestingly, the risks of learning deficits in children delivered with cesarean section under general anesthesia were higher compared with cesarean deliveries under regional anesthesia.

In a large-population study, DiMaggio *et al.* [19] focused on assessing learning disabilities in 93,317 patients. Again, it was found that children who had received anesthesia before the age of 3 years required greater use of Medicaid services to deal with learning deficits than did children who had not been exposed to anesthesia. Kalkman *et al.* [20], in The Netherlands, looked at a smaller population of patients who had been exposed to anesthesia very early in life and found a higher incidence of learning deficits during school years.

Several studies of premature infants have suggested that behavioral disabilities later in life are more prevalent among those who were exposed to surgery and general anesthesia during the neonatal period than among premature infants who were treated medically. For example, surgically treated premature infants with patent ductus arteriosus [21] or necrotizing enterocolitis [22] had worse neurological outcomes than did premature infants who were treated medically. Although a possible causal link between early exposure to general anesthesia and neurocognitive deficits could be suggested on the basis of these studies, a measure of caution is advisable since the effects of surgery cannot be clearly separated from the effects of anesthesia. Also, there is the fact that congenital abnormalities requiring surgical intervention were associated with significant comorbidities, which could have contributed to the observed behavioral deficits. In support of this notion is a recently published retrospective clinical study that examines the possible causal relationship between anesthesia administration and cognitive impairments in monozygotic twins exposed to anesthesia either before the age of 3 years or from 3 to 12 years of age [23]. Results have shown that twins who were exposed to anesthesia before the age

of 3 had significantly lower educational achievement scores and significantly more cognitive problems than twins not exposed to anesthesia. Interestingly, though, the exposed twin did not differ from the non-exposed twin, suggesting that the underlying genetic vulnerability of the individual to learning disability is likely correlated with the reason for the surgery for which anesthesia was administered. The authors conclude that early exposure to anesthesia is a marker of an individual's vulnerability for later learning problems, regardless of their exposure to anesthesia.

### Implications for clinical practice

Although, to date, some clinical studies suggest that the exposure of young children to surgery and general anesthetics may cause significant neurocognitive deficits and a variety of behavioral sequelae, those studies were done retrospectively [12-25] and therefore could not control for the many variables that come into play during the perioperative period. However, the complex issues associated with the design of randomized double-blinded prospective clinical studies of very young patients cannot be underestimated. These issues include, but are not limited to, ethical considerations; the lack of biomarkers of apoptosis that can safely be used in a living organism; the complexity and meaningfulness of various clinical outcomes, especially neurocognitive ones; and the lack of appropriate controls.

Although it is too early to tell what implications these findings may have on pediatric anesthesia practice, it is of paramount importance to relentlessly pursue a better grasp of poor neurocognitive outcomes that could be anesthesia-induced. Even though the majority of clinically used general anesthetics have been shown to induce developmental neurodegeneration, it appears that the timing and duration of anesthesia exposure play important roles, thus suggesting that age, rather than the choice of anesthesia, may be the main risk factor in anesthesia-induced developmental sequelae.

Since the use of anesthetics in obstetric and pediatric anesthesia is a necessity that cannot be avoided when pregnant mothers and newborn infants present with life-threatening conditions requiring surgery or a prolonged sedation in the intensive care unit (or both), it is imperative that we improve our understanding of the mechanisms that underlie the neurotoxicity of anesthetic agents. Though still in a very early stage, we are well on the way to developing ways of preventing anesthesia-induced developmental neurotoxicity so that existing anesthetics can be used to their full advantage for therapeutic benefits without the risk of neurotoxic side effects.

### Competing interests

The author declares that she has no competing interests.

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