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Early childhood general anaesthesia exposure and neurocognitive development

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Key points

- Preclinical evidence indicates anaesthetic exposure in neonatal animals leads to neurotoxicity and neurobehavioural deficits.
- Available clinical studies related to anaesthetic neurotoxicity are retrospective and inconclusive.
- Two multicentre clinical studies are currently underway to address anaesthetic neurotoxicity in children.

Summary. A great deal of concern has recently arisen regarding the safety of anaesthesia in infants and children. There is mounting and convincing preclinical evidence in rodents and non-human primates that anaesthetics in common clinical use are neurotoxic to the developing brain *in vitro* and cause long-term neurobehavioural abnormalities *in vivo*. An estimated 6 million children (including 1.5 million infants) undergo surgery and anaesthesia each year in the USA alone, so the clinical relevance of anaesthetic neurotoxicity is an urgent matter of public health. Clinical studies that have been conducted on the long-term neurodevelopmental effects of anaesthetic agents in infants and children are retrospective analyses of existing data. Two large-scale clinical studies are currently underway to further address this issue. The PANDA study is a large-scale, multisite, ambi-directional sibling-matched cohort study in the USA. The aim of this study is to examine the neurodevelopmental effects of exposure to general anaesthesia during inguinal hernia surgery before 36 months of age. Another large-scale study is the GAS study, which will compare the neurodevelopmental outcome between two anaesthetic techniques, general sevoflurane anaesthesia and regional anaesthesia, in infants undergoing inguinal hernia repair. These study results should contribute significant information related to anaesthetic neurotoxicity in children.

Keywords: anaesthesia, paediatric; children; neurocognitive outcome; neurotoxicity; risk

An estimated 6 million children receive anaesthesia annually in the USA.[1] Among infants, defined as those under 12 months of age, the Nationwide Inpatient Sample data indicate that 1.5 million undergo surgery as inpatients each year in the USA. Surgical anaesthesia provides amnesia, analgesia, immobility, and control of autonomic responses during surgical procedures. In the non-surgical setting, anaesthesia in children provides safe and appropriate conditions for interventional procedures, imaging studies, and diagnostic procedures. The benefits of anaesthesia in children include alleviation of pain, anxiety, maintaining stable vital signs, and providing adequate conditions for surgery or the procedures in question. These benefits have accounted for the exponential increase in the number of anaesthetics administered to children in many different settings, for many different procedures, and to children of increasingly younger age.

The widespread and growing use of anaesthesia in infants and young children thus makes its safety a major public health issue of interest to the public, government agencies, and the anaesthesia community. This issue has become a matter of great concern with the evidence that anaesthetics are neurotoxic in animal studies.

A conceptual framework for research related to the adverse health effects of anaesthesia exposure *in vivo*, *in vitro*, and *in populo* is presented in Figure 1. The goal of this review is to provide an overview of available clinical studies related to neurocognitive development and early childhood exposure to anaesthesia, including the outline of two large-scale ongoing clinical studies. The review only briefly summarizes the preclinical studies that have reported functional outcomes, which serve as important background information to the clinical studies. For a more comprehensive review of all of the preclinical studies on anaesthetic neurotoxicity, the reader is referred to other recent reviews.[2–6]

Preclinical studies of anaesthetic neurotoxicity in the developing brain

Experimental studies in animals (rats, mice, guinea pigs, piglets, and non-human primates) have shown that exposure of the developing mammalian brain to a variety of commonly used anaesthetic agents during critical developmental periods can lead to neuronal apoptosis or neurodegeneration

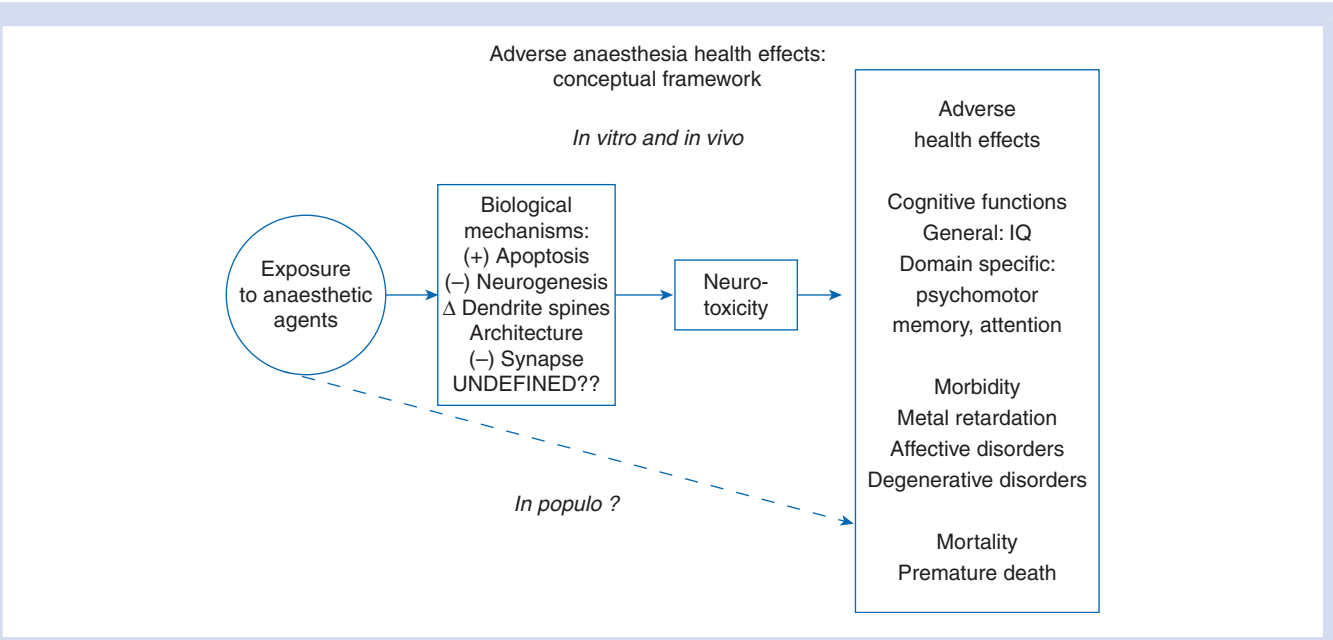

Fig 1 A conceptual framework in studying anaesthetic neurotoxicity (originally conceived by Dr Guohua Li, MD, DrPH, Columbia University).

in vitro and measureable neurobehavioural and functional deficits *in vivo*.[2–4 7–53]

Ikonomidou and colleagues[22] first made the observation that *N*-methyl-D-aspartate glutamate receptor (NMDAR) antagonists induced extensive neuronal apoptosis in the developing rat brain. This has potentially important implications for clinical paediatric and obstetric anaesthesia since certain clinically used anaesthetic agents have similar mechanisms of action as NMDAR antagonists.[22] The concern was thus raised with respect to the potential neurotoxic effects of other anaesthetic agents. Subsequently, studies by Jevtovic-Todorovic and colleagues[7] and Fredriksson and colleagues[20] found the same pattern of *in vitro* neuronal apoptosis after exposure of the developing rat brain to anaesthetic agents that act as NMDAR antagonists and γ-aminobutyric acid type A receptor (GABAR) agonists. Jevtovic-Todorovic and colleagues[7] exposed rats at postnatal day 7 to a 'cocktail' of clinically used anaesthetic agents (midazolam, isoflurane, and nitrous oxide) and demonstrated not only neuronal apoptosis in the infant rat brain, but also persistent functional deficits in memory and learning in juvenile rats, with impairment of both spatial reference and working memory in adult rats.

Dose-dependent neuronal apoptosis in response to anaesthetics has been documented in both rodent and non-human primate studies. Ketamine induces neuronal apoptosis and neurodegeneration in both rats and monkeys with high doses, prolonged exposure, or repeated doses.[2 3 49 50 52] Similar dose-dependent effects have been documented for propofol and isoflurane.[3 20 37] Neurotoxic effects were more prominent when the exposure was to a combination of anaesthetic agents with both NMDAR and GABAR actions than from exposure to an agent with either NMDAR or GABAR actions alone.

Another important feature of anaesthetic neurotoxicity is that there is a critical period of vulnerability for exposure. Studies in rodents found neuronal apoptosis to be the greatest if exposure occurred at postnatal day 7, the period of peak synaptogenesis.[10 50] In non-human primates, exposure occurring at postnatal day 5, but not at postnatal day 35, was found to cause neurotoxicity.

These preclinical studies indicate that neurotoxicity of anaesthetic agents in the developing brain, as evidenced by neuronal apoptosis and necrosis, is greatest if the exposure occurs during periods of peak synaptogenesis, with high doses or with a combination of anaesthetic agents. However, anaesthetic-induced neurotoxic effects involve more than neuronal apoptosis and necrosis during synaptogenesis. Several recent studies suggest that anaesthetics also inhibit neurogenesis and alter the development of dendritic spine architecture, important developmental processes in synapse formation 0.[17 53] Although much work remains to be done to elucidate the specific mechanisms of anaesthetic neurotoxicity, much progress has been made. One proposed mechanism is the inhibition of brain-derived neurotrophic factor (BDNF) signalling pathways by GABAergic and NMDAR-acting anaesthetic agents.[25 53] BDNF has also been shown to be involved in the developmental neurotoxicity observed with lead exposure.[54]

Most preclinical studies have examined the effects of various anaesthetics on histopathological changes *in vitro*. The focus of the present review is on those studies that also examined functional outcomes (Table 1).[7 9–13 20 24 45] To date, functional outcome studies have only been performed in rats and mice. Preliminary findings in non-human primates have been reported at meetings, but are not yet published. Although studies have consistently demonstrated