Anesthesia-induced developmental neurotoxicity in children: past, present, and future

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Since 1999, a large body of evidence from various animal models indicates a link between anesthesia exposure in early stage of life and subsequent neurodevelopmental impairments[1]; namely, almost all commonly used intravenous and inhalational anesthetics, including gamma-aminobutyric acid agonists and N-methyl-D-aspartate antagonists, can induce dose- and age-dependent neuronal apoptosis and death *in vitro*. Moreover, abundant data from nematodes to primate animals have shown a variety of anatomic and neurodevelopmental sequelae from anesthesia exposure in young animals.[2,3] In the rodents, the most prominent manifestations of anesthesia-induced developmental neurotoxicity (AIDN) are often observed at post-natal day 7, which is the peak period for synaptogenesis. In animal models, both single and multiple anesthesia exposures can affect neurodevelopment. Also, the duration and timing of anesthesia exposure are the important influencing factors of AIDN.[4] Alarmingly, these neurotoxic effects by neonatal exposure to anesthesia may result in the long-term detrimental functional outcomes in later childhood or adulthood, such as deficits in memory, learning, attention, and motor function.[2]

According to the published data, the possible mechanisms of AIDN in the immature brain include generation of reactive oxygen species and energy breakdown, activation of apoptosis via extrinsic or intrinsic pathway, inhibition of neurotrophic factors (eg, brain-derived neurotrophic factor) and neurogenesis, neuroinflammation, negative influence on synaptogenesis, changes of receptor expression and neuronal excitability, damage of neuronal and glial cytoarchitecture, change of neuronal plasticity, and others.[2] However, the relative importance of each of these mechanisms is unclear. Moreover, it is difficult to extrapolate the results of basic experiments to human infants because of several reasons. First, compared to animals, the structures of the human brain are more complex and the development stage of the human brain is much longer.[5] Second, one of the important limitations of available evidence from basic experiments is the lack of consensus on pre-clinical models, and ages and durations of anesthesia exposure. Furthermore, the measurement methods used for the determination of neurodevelopmental outcomes are not standardized. Third, unlike the human studies, animal exposure to anesthesia is poorly monitored and the detailed assessment regarding physiological impacts of anesthesia is significantly insufficient.

Recently, a population-based birth cohort study regarding the utilization of general anesthesia in children shows that one in seven children undergo at least one anesthesia prior to the age of 3 years, and approximately one in four children receiving general anesthesia falls within the high-risk category as defined by the recent America Food and Drug Administration warning.[6] As the clinical significance of AIDN remains uncertain, this issue has been widely discussed and concerned in the popular media, and surgeons can expect many questions from worried parents of pediatric patients.[7] Thus, it is necessary to specify the possible limitations of existing clinical evidence regarding AIDN.

(1) Retrospective studies: to date, clinical evidence regarding AIDN is mainly from the retrospective observational studies and the results about the relationship between anesthesia exposure and adverse neurodevelopmental outcomes are mixed. Hansen *et al*[8] demonstrate no significant association of single anesthesia exposure with post-operatively neurodevelopmental deficits. Furthermore, the study of Wilder *et al*[9] indicates that only multiple anesthesia exposures are associated with adverse neurodevelopmental outcomes. In the study of Ing *et al*[10]; however, a single anesthesia exposure causes post-operatively neurocognitive impairments. The validity of retrospective

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findings is limited because of many potential confounders, such as pre-existing conditions, surgical diagnoses, inflammatory and pain response to surgery, and unmeasured peri-operative physiological parameters.[11]

(2) Recent well-designed clinical trials: since 2016, several rigorous clinical studies on AIDN, for example, the pediatric anesthesia and neurodevelopmental assessment (PANDA) study,[12] the general anesthesia compared to spinal anesthesia (GAS) study,[13,14] and the Mayo anesthesia safety in kids (MASK)[15] study, have been published. The characteristics, designs, main results, and conclusions of these studies are summarized in Supplementary Table 1, http://links.lww.com/CM9/A75.

The PANDA study is a sibling-matched cohort study determining if a single anesthesia exposure is associated with impaired neurocognitive development and abnormal behavior in later childhood. It included 105 sibling pairs within 36 months in age and currently 8 to 15 years old. A single exposure to inhaled general anesthesia with durations of 20 to 240 min was given during inguinal hernia surgery in the exposed siblings and no anesthesia exposure was provided in the unexposed siblings, before age 36 months. The global cognitive function assessment was used as the primary outcome. The results showed no statistically significant differences in mean neurocognitive scores between sibling pairs in memory/learning, motor/processing speed, visuospatial function, attention, executive function, language, or behavior.[12]

The GAS study is an international assessor-masked randomized controlled trial (RCT) including two parts.[13,14] The first part was performed on the infants younger than 60 weeks post-menstrual age, born at greater than 26 weeks' gestation, and who had inguinal herniorrhaphy. Infants were randomly assigned to receive awake-regional anesthesia ($n = 238$) or sevoflurane-based general anesthesia ($n = 294$). By assessing composite cognitive score at 2 years of age, the results indicated that compared with awake-regional anesthesia, less than 1 h of sevoflurane anesthesia did not result in an increased risk of adverse neurodevelopmental outcomes.[13] The second part of the GAS study was carried out on the same infants of the above first part and the primary outcome measure was the full-scale intelligence quotient on the Wechsler Preschool and Primary Scale of Intelligence at 5 years of age. Based on outcome data obtained from 205 children receiving awake-regional anesthesia and 242 receiving sevoflurane anesthesia, less than 1 h of sevoflurane anesthesia in early infancy did not alter neurodevelopmental outcomes at age 5 years compared with awake-regional anesthesia in a predominantly male study population.[14]

The MASK study is the first clinical trial assessing the effects of both single and multiple anesthesia exposures before age 3 years on neurodevelopmental outcomes. The primary outcome was the full-scale intelligence quotient standard score of the Wechsler Abbreviated Scale of Intelligence and secondary outcomes included the individual domains from a comprehensive neuropsychological assessment and parent reports. The neuropsychological tests were performed at ages 8 to 12 or 15 to 20 years. A total of 997 children completed testing; of them, 411, 380, and 206 were unexposed, singly exposed, and multiply exposed to anesthesia, respectively. The results demonstrated that anesthesia exposure before age of 3 years was not associated with deficits in the primary outcome of general intelligence, but multiple anesthesia exposures were possibly associated with modest decreases in processing speed and fine motor coordination. Thus, it is concluded that only multiple anesthesia exposures, but not single anesthesia exposure, are associated with a pattern of changes in specific neuropsychological domains that are associated with behavioral and learning difficulties.[15]

The above several high-quality clinical trials have provided some evidence about AIDN, but more well-designed RCTs still are needed to obtain exact answers to this complex issue.

The greatest challenge to studying AIDN may be differentiating direct toxic effects of anesthetics on the developmental brain from adverse effects of other indirect reasons such as peripartum and peri-operative risk factors. In fact, surgery represents a complex exposure of serial risk factors and anesthesia exposure may only be one of the risk components. Thus, it is difficult to determine whether post-operative adverse neurodevelopment outcomes are attributable to anesthesia exposure or other factors.[16]

Another challenge may be a lack of standardization both in animal studies and clinical studies regarding AIDN. In the available literature, there are significant differences in timings, doses, and duration of anesthesia exposure, assessment of neurodevelopmental outcomes and follow-up periods among various studies. Undoubtedly, these heterogeneities among different studies can make the interpretation and extrapolation of findings very difficult.

As proper design and implementation of an RCT can result in convincing causal inferences, it is generally considered as the first level of evidence to assess the efficacy of novel interventions/therapies.[13] When a placebo-controlled RCT to assess AIDN is designed; however, it poses significant ethical challenges because both surgeries without anesthesia and anesthesia without surgery are not ethical or acceptable options. It will be even more impossible if prolonged or repeated anesthesia exposures are studied.

Prospective RCTs that can accurately determine anesthesia exposure, rigorously control for confounders and follow up neurodevelopmental outcomes into adolescence are suggested. Furthermore, it needs further animal studies to characterize the detailed mechanisms of AIDN. During clinical and basic researches, physiological parameters, doses and exposure times of anesthetics, the subtle neurotoxic assessment must be carefully controlled. Especially, outcomes should be measured by trained, blinded assessors using a comprehensive battery of developmental assessments. To distinguish long-term neurotoxic effects of anesthesia exposure from short-term

changes, it must be emphasized that the time interval between anesthesia exposure and first neurodevelopmental assessment should be sufficiently long; the usual recommendation is at least over 6 months.[17]

As the exact mechanisms and the extent of the potential risk for neurotoxicity from anesthesia exposure remain unclear, in some cases, careful consideration should be taken to prevent and attenuate the neurotoxic damage caused by anesthesia exposure. Delaying elective procedures until children are older, avoiding unnecessary tests that require general anesthesia, encouraging non-anesthesia procedures when feasible, are all useful techniques. Moreover, the use of multiple anesthetics with different mechanisms of action for necessary surgeries can also reduce the total doses of anesthetics.[5] Anesthesiologists play a role in minimizing anesthesia exposure for pediatric patients. Most important, future studies should be aimed at determining the exact mechanisms of AIDN and obtaining useful approaches to ameliorate adverse neurodevelopmental outcomes.

Data from animal experiments have provided ample evidence that general anesthetics can cause neurotoxic changes of developing brain. In contrast, the recent high-qualified MASK, PANDA, and GAS studies show that a single exposure to general anesthesia lasting less than 1 h in early infancy is not associated with an increased risk of neurodevelopmental deficits in later childhood. Thus, most experts would agree that single, brief anesthesia exposure in early infancy does not result in a significantly neurodevelopmental defect. Nevertheless, these studies still leave important issues unsolved. Most important, it remains unclear whether a longer anesthesia exposure or multiple anesthesia exposures are associated with subsequent neurodevelopmental defects.

It is both a responsibility and an opportunity for specialties such as anesthesiology, surgery, and neurology to work together to address this critical public health issue closely related to clinical anesthesia of pediatric and pregnant patients until a clear solution about the source of this potential harm to the developing brain is obtained.

Conflicts of interest

None.

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