Does General Anesthesia Have Detrimental Effects on Immature Human Brain?
Si-Meng Liu, An-Shi Wu, and Yun Yue

ABSTRACT

Aim of review: Early life exposure to general anesthesia in preclinical studies has consistently led to neurodevelopmental deficits later in life. However, the transferability of animal data to humans is questioned, and the published clinical results remained controversial. In this review, we attempt to summarize the most current data in human studies, as well as reveal how the research types have changed over the years.

Method: We searched the PubMed database for the keywords “children” or “pediatric” or “neonatal” or “immature brain” or “neurodevelopment” combined with the keywords “anesthesia neurotoxicity”. High-quality original studies of the past decade were selected and divided into animal experiments, retrospective cohort studies and prospective clinical trials to analyze respectively.

Recent findings: Laboratory studies have suggested that commonly used anesthetic agents produce profound neurotoxic effects. Retrospective cohort studies found mixed results which may depend on different outcome measures. Some of them suggested anesthetic exposure was associated with poor neurodevelopmental outcome, but not causality. Most well-conducted clinical trials including PANDA (General Anesthesia compared to Spinal Anesthesia) and GAS (Pediatric Anesthesia and Neurodevelopment Assessment) suggested encouraging results that there is no significant neurocognitive deficit for single or brief anesthetic exposure early in life. The effect of anesthesia neurotoxicity may be time-dependent which remains to be proved.

Summary: A majority of well-designed studies provide some reassurance regarding single or brief anesthetic exposure on immature human brain, but many questions surrounding early anesthesia and cognition remain unanswered. So far, surgeons, anesthesiologists, and parents should be careful, as far as possible to reduce the number and duration of children exposed to anesthetics. Elective surgeries should be delayed to more than 3 years of age. (Funded by the National Natural Science Foundation of China.)
General anesthesia providing amnesia, unconsciousness, immobility, and control of sympathetic responses allows millions of infants and children to undergo life-saving surgery and other essential surgical or medical procedures each year. In the recent decades, a large number of laboratory studies and animal experiments have demonstrated that general anesthetics may be neurotoxic to immature brain, resulting in adverse neurodevelopmental outcomes later in life (1-10). Based on the results of animal studies, concerns have been raised that anesthesia may be harmful for developing human brain. However, the published results remained controversial (11, 12). In this review, we attempt to summarize the most current data in human studies, as well as reveal how the research types have changed over the years.

1990s and Early 2000s: Laboratory Animal Experiments Have Suggested Anesthetic Neurotoxicity

Compared with mature neurons, immature neurons seem to be relatively sensitive to toxic substances. In the 1990s and early 2000s many in-vivo and in-vitro laboratory studies have suggested that commonly used anesthetic agents produce profound neurotoxic effects in a wide variety of immature animal species, including rodents and nonhuman primate (13, 14). Implicated drugs involved N-methyl-D-aspartate (NMDA) receptor antagonists (eg. ketamine, nitrous oxide) (2, 3, 5, 8) and γ-aminobutyric acid (GABA) agonists (2, 4-7, 10) (eg. benzodiazepines, barbiturates, propofol, etomidate, volatile anesthetics). Exposure to these anesthetics in early life may cause histologic changes such as widespread neuron and oligodendrocyte apoptosis, changes in neuronal morphology, a reduction in trophic factors, alterations in synaptic density and dendritic architecture, and impaired neurogenesis in the hippocampus (9). The cell death has been proved to be triggered through translocation of Bax proteins on mitochondrial membranes causing leakage of cytochrome-c culminating in activation of caspase-3 (15). Although, a correlation of neonatal brain cell death with long-term abnormalities in neurological function and brain structure is hard to demonstrate, some studies found behavioral abnormalities and temporary learning impairment in anesthetic exposed animals (1, 4, 5).

Factors that influence the extent of injury include age at the time of drug exposure and cumulative anesthetic dose (9, 15). While many of the initial studies established that the window of vulnerability to these agents coincides with the peak developmental period for synaptogenesis, also known as the “brain growth spurt” period, which in rodents occurs primarily at postnatal day 7, but more recent research has shown that anesthetic neurotoxicity risk extends beyond this window (16).

Late 2000s and 2010s: Retrospective Cohort Studies Found Mixed Results

Alarming findings from animal experiments during the last two decades have raised substantial concerns that similar effects may also occur in the developing human brain. However, the applicability of these animal data to humans undergoing anesthesia in early life remains to be proved (17).

The transferability is questioned by some reasons. First, because of the brain growth spurt period and its overall length varying significantly between humans and animal models (in rodents it occurs primarily at postnatal day 7, but in humans extends from the middle of pregnancy and lasts at least up to the second year of life), the anesthetics influences a exaggeratedly longer time period of neurogenesis in animals than in humans. Second, the anesthetic susceptibility of animal and human brains is different, and animals always require considerably larger anesthetic concentrations. Third, the potential lack of control over physiological factors and vital signs in laboratory studies can lead to sustained metabolic acidosis, hypoglycaemia and hyperkalaemia, all of that might induce neuronal apoptosis in themselves (7).

In the past decade, numerous observational studies have been published. We searched the PubMed database for the keywords “children” or “pediatric” or “neonatal” or “immature brain” or “neurodevelopment” combined with the keywords “anesthesia neurotoxicity”. After excluding review articles and animal studies we selected original studies which of sufficient quali-
does not rely in this review (Table). All of them originated from different population-based birth cohorts around the world.

Viewing these published articles, we can find out that the mixed results may depend on the outcome measures which commonly include International Classification of diseases-9th Revision (ICD-9) diagnosis code for behavioral and developmental disorders or language and cognitive disorders, learning disability, academic performance and neuropsychological assessments. Studies relied on academic achievement scores or the incidence of behavior disorders tended to publish negative results. For example, the two Danish studies (25, 26) and the Netherlands monozygotic twin pairs study (18) all suggested that exposed to anesthesia or surgery in the early time of life didn’t make academic performance significant different in adolescence. Flick RP et al. (23) found that repeated exposure to anesthetic and surgery prior to age 2 was a significant independent risk factor for the later development of learning disabilities but did not affect the school test scores or the incidence of emotional or behavior disorders in 19-years old. Ing C et al. (27, 28) used different outcome to measure the same cohort and indicated that academic performance may lack of sensitivity to found neurodevelopment deficits, in contrast, directly administered neuropsychological assessments particularly in the domains of language and cognition might have increased sensitivity to capture subtle effects that may be difficult to detect clinically. Another study also proved that deficit in language and cognition was associated with exposure to anesthesia and surgery before the age of 3, but children with broad neurodevelopment delay or primarily behavioral deficits were not associated with anesthesia neurotoxicity (31).

Almost all the epidemiologic studies primarily focused on exposures occurring under 3 years of age because of human brain growth spurt period being considered to extend through age 3 years. There was one study using data from Raine Study to investigate whether children with initial anesthetic exposure after 3 years old can also suffer from neurodevelopment deficits (29). It showed that although initial exposure to anesthesia after age 3 had no measurable effects on language or cognitive function, decreased motor function was found. These results suggested that there may be distinct windows of vulnerability for different neurodevelopment domains in children.

The effect of anesthesia neurotoxicity to the immature brain was considered to be time-dependent. Several studies from different cohorts all indicated that only exposure to multiple anesthesia or cumulative anesthesia duration of more than 120min can increase the risk of neurodevelopment disorders (20, 21, 23). A single or brief exposure to anesthetic drugs did not adversely affect long-term neurodevelopment outcomes (20, 22, 23). However, there also were some studies suggested once or multiple exposed to anesthesia both increased long-term risk of clinical deficits in language, cognitive or behavioral disorders (19, 27).

So far, some retrospective cohort studies have found an association between exposure to anesthesia in early childhood and increased risk of poor neurodevelopmental outcome, which fits with preclinical animal data well. Conversely, some cohort studies have found no evidence for an association. The mixed results may contribute to the research type itself. It is because that the retrospective cohort studies are confounded by multiple factors such as large and diverse populations, heterogeneity of exposure time, anesthetic drugs used, or doses or combination of drugs used, the effects of comorbidity and the impact of the surgical procedure cannot be separated from the effects of anesthesia, which inherently limit the capacity for cohort studies to establish the link between exposure to anesthesia and neurodevelopment outcome (32). Bartels M et al. (18) found that when used monozygotic twin pairs to minimize the confounding variables from environments and genetic predisposition, childhood anesthetic exposure did not have direct causal effect on cognitive performance. Furthermore, one of whose co-twins receives anesthesia by age 12 have significantly poorer learning-related outcomes than twins from pairs where neither received anesthesia by age 12. The finding revealed that children who are likely to undergo surgery early in life might have underlying genetic vulnerability to learning disabilities. That is, children who are sick receive surgery. Children who receive surgery receive anesthesia. Children who are sick often al-
<table>
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<tr>
<th>Study cohort</th>
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<th>Hazard ratio (95%)</th>
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<tr>
<td>Young-Netherlands Twin Register (YNTR) includes monozygotic twin pairs born between 1986 and 1995</td>
<td>Concordant non-exposed/discordant/concordant exposed</td>
<td>1143 pairs</td>
<td>Not mentioned</td>
<td>0-3-year old</td>
<td>1) Educational Achievement (EA) assessed with the Dutch CITO-elementary test; 2) Cognitive Problems/Inattention (CP) based on the Conners’ Teacher Rating Scale</td>
<td>No difference in EA or the incidence of CP in the discordant group; the incidence of learning disabilities was higher in pairs of twins in whom one underwent anesthesia compared with the set of twins of where neither was exposed</td>
<td>Not mentioned</td>
<td>Bartels M et al. 2009 (18)</td>
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<tr>
<td>New York state Medicaid Analytic Extract (MAX), files from 1999 to 2002</td>
<td>Children underwent inguinal hernia repair/who did not have hernia</td>
<td>383/5050</td>
<td>Inguinal hernia repair</td>
<td>0-3-year old</td>
<td>≤4-year old</td>
<td>ICD-9 diagnosis code for behavioral/developmental disorders</td>
<td>A single anesthetic exposure increased incidence of developmental or behavioral disorders</td>
<td>2.3(1.3, 4.1)</td>
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<tr>
<td>New York state Medicaid Analytic Extract (MAX), files from 1999 to 2005</td>
<td>Children who had surgical or anesthetic exposure/who did not have</td>
<td>304 (210 for single exposure/71 for 2 exposures/23 for ≥3 exposures)</td>
<td>Inguinal hernia repair; Repair of gastroschisis; Exploratory laparotomy; Appendectomy; Pyloromyotomy; Tonsillectomy/Adenoidectomy; Partial small bowel resection; Hemicolectomy, etc.</td>
<td>0-3-year old</td>
<td>≤4-year old</td>
<td>ICD-9 diagnosis code for behavioral/developmental disorders</td>
<td>≥2 anaesthetic exposures increased incidence of developmental or behavioral disorders</td>
<td>1.1(0.8, 1.4) for single exposure/2.9 (2.5, 3.1) for 2 exposures/4.0(3.5, 4.5) for ≥3 exposures</td>
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<td>Study cohort</td>
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<td>Population-based birth cohort in Olmsted Country, Minnesota from 1976 to 1982</td>
<td>Children received general anesthesia/ who did not have</td>
<td>Cardiac surgery; Ear nose and throat surgery; General surgery; Neurosurgery; Ophthalmology; Oral surgery; Orthopedics; Plastic surgery; Urology; etc.</td>
<td>593 (449 for single exposure/ 100 for 2 exposures / 44 for ≥ 3 exposures ) /4764</td>
<td>Learning Disabilities (calculated with a formula using Wechsler IQ scales and Woodcock Johnson achievement tests)</td>
<td>≥2 anesthetic exposures or cumulative anesthesia duration of more than 120 min significantly increases the incidence of LDs</td>
<td>1.0(0.75, 1.27) for single exposure/ 1.59 (1.06, 2.37) for 2 exposures/ 2.60 (1.64, 4.24) for ≥3 exposures</td>
<td>Wilder RT et al. 2009 (21)</td>
<td></td>
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<tr>
<td>Population-based birth cohort in Olmsted Country, Minnesota from 1976 to 1982</td>
<td>General anesthesia for Cesarean delivery/ regional anesthesia for Cesarean delivery/ Spontaneous vaginal birth</td>
<td>Cesarean delivery</td>
<td>193/304/ 4823</td>
<td>Learning Disabilities (calculated with a formula using Wechsler IQ scales and Woodcock Johnson achievement tests)</td>
<td>Children exposed to anesthesia during Cesarean delivery are not more likely to develop LDs. Brief perinatal exposure to anesthetic drugs dose not adversely affect long-term neurodevelopment outcomes</td>
<td>0.88(0.59, 1.31) general anesthesia/ 0.64(0.44, 0.92) regional anesthesia</td>
<td>Sprung J et al. 2009 (22)</td>
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<td>Population-based birth cohort in Olmsted Country, Minnesota from 1976 to 1982</td>
<td>General anesthesia before age 2/ no anesthetic exposure</td>
<td>Not mentioned</td>
<td>350 ( 286 for single exposure/ 64 for multiple exposures ) /700</td>
<td>1) LDs; 2) Receipt of an individualized education program for an emotional/ behavior disorder (IEP-EBD); 3) Scores of group-administered achievement tests</td>
<td>Repeated exposure to anesthesia and surgery before the age of 2 was a significant independent risk factor for the later development of LDs but not the need for educational interventions related to emotion/ behavior</td>
<td>1.06(0.77, 1.46) for single exposure/2.12 (1.26, 3.54) for multiple exposures of school test score</td>
<td>Flick RP et al. 2011 (23)</td>
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<td>Study cohort</td>
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<tr>
<td>Population-based birth cohort in Olmsted Country, Minnesota from 1994 to 2007</td>
<td>General anesthesia before age 2/no anesthetic exposure</td>
<td>Not mentioned</td>
<td>350 (286 for single exposure/ 64 for multiple exposures ) 5007</td>
<td>0-2-year old</td>
<td>19-year old</td>
<td>Attention deficit/hyperactivity disorder (ADHD)</td>
<td>Repeated exposure to anesthesia and surgery before the age of 2 was at increased risk for the later development of ADHD</td>
<td>1.18(0.79, 1.77) for single exposure/1.95 (1.03, 3.71) for multiple exposures</td>
</tr>
<tr>
<td>Danish Birth Cohorts which includes all children born in Denmark from 1986 to 1990</td>
<td>Inginal hernia repair/randomly selected 5% population sample</td>
<td>Ingual hernia repair</td>
<td>2689/ 14575</td>
<td>0-1-year old</td>
<td>15-16-year old</td>
<td>1) The average test score at 9th grade; 2) The proportion not attaining the test scores</td>
<td>Exposed to anesthesia/surgery didn't make significant differences in test scores, but increased nonattainment suggests a subgroup of exposed</td>
<td>1.18(1.04, 1.35) of test score nonattainment</td>
</tr>
<tr>
<td>Danish Birth Cohorts which includes all children born in Denmark from 1986 to 1990</td>
<td>Pyloromyotomy /randomly selected 5% population sample</td>
<td>Pyloromyotomy</td>
<td>779/ 14865</td>
<td>≤3-month age</td>
<td>15-16-year old</td>
<td>Children is developmentally disadvantaged</td>
<td>Once or multiple exposed to anesthesia both increased long-term risk of clinical deficit in receptive and expressive language as well as abstract reasoning</td>
<td>1.37(1.11, 1.68) of test score nonattainment</td>
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<tr>
<td>Western Australian Pregnancy Cohort (Raine) Study includes 2868 children born from 1989 to 1992</td>
<td>Anesthetic exposure/none</td>
<td>Myringotomy; Inguinal and umbilical hernia; Circumcision; Tonsillectomy and adenotonsillectomy; Dental procedure; Minor skin and nail procedure; Orchiopey, hydrocele and varicocele; Procedure on</td>
<td>321/2287</td>
<td>0-3-year old</td>
<td>10-year old</td>
<td>Neropsychological test including Clinical Evaluation of Language Fundamentals (CELF), Raven's Colored Progressive Matrices Cognition (CPM)</td>
<td>Once or multiple exposed to anesthesia both increased long-term risk of clinical deficit in receptive and expressive language as well as abstract reasoning</td>
<td>2.36(1.47, 3.79) for single exposure/ 2.68 (1.07, 6.72) for multiple exposures of CELF; 1.73(1.04, 2.88) for single exposure/1.92(0.81, 4.55) for multiple exposures of CPM</td>
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<tr>
<td>Study cohort</td>
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<tr>
<td>Western Australian Pregnancy Cohort (Raine) Study includes 2868 children born from 1989 to 1992</td>
<td>Anesthetic exposure/ none</td>
<td>extraocular muscles; Hypo/epispadias repair and chordee release; Nasolacrimal duct probe, etc.</td>
<td>112/669</td>
<td>0-3-year old</td>
<td>10-year old</td>
<td>1) Neuropsychological test; 2) ICD-9 code language and cognitive disorders; 3) Academic achievements tests</td>
<td>Neropsychological test and ICD-9 code outcomes showed an increased risk of deficit in exposed children whereas academic achievement scores did not</td>
<td>2.47(1.41, 4.33)</td>
</tr>
<tr>
<td>Western Australian Pregnancy Cohort (Raine) Study includes 2868 children born from 1989 to 1992</td>
<td>Anesthetic exposure between ages 3 and 5 years/ anesthetic exposed between ages 5 and 10 years/ children unexposed before age 10</td>
<td>Myringotomy; Tonsillectomy and adenoidectomy; Tonsillectomy and adenoidectomy; Minor skin and nail procedure; Nasal or sinus procedure; Circumcision; Appendectomy, etc.</td>
<td>80/45/1140</td>
<td>3-5-year old/5-10-year old</td>
<td>10-year old</td>
<td>1) Neropsychological test including CELF and CPM; 2) McCarron Assessment of Neuromuscular Development (MAND) motor function scores</td>
<td>Children initially exposed to anesthesia over age 3 did not have an increased risk of neurodevelopmental deficits in language and abstract reasoning at age 10, but motor deficit was found</td>
<td>2.32(1.42, 3.79)</td>
</tr>
<tr>
<td>National Health Insurance Research Database of Taiwan Children includes 16465 children born from 2001 to 2005</td>
<td>General anesthesia exposure before ages 3/ unexposed</td>
<td>Not mentioned</td>
<td>3293/91790</td>
<td>0-3-year old</td>
<td>5-10-year old</td>
<td>Attention deficit/hyperactivity disorder (ADHD)</td>
<td>Exposure to general anesthesia before 3 years of age was not associated with ADHD</td>
<td>1.06(0.86, 1.31)</td>
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</table>
so have learning disabilities. The hypothetical causal link between anesthesia and later learning problems may be on the basis of laboratory work is not supported by these data.

With insufficient data to draw any firm conclusions about an association between exposure to anesthetics and subsequent adverse neurodevelopmental outcomes in children, further prospective randomized controlled researches are needed to better define the association.

**Prospective Clinical Trials Are in Progress**

In 2009 the United States Food and Drug Administration (FDA) established a public-private partnership with the International Anesthesia Research Society (IARS) called SmartTots (Strategies for Mitigating Anesthesia-Related Neurotoxicity in Tots) (http://smarttots.org) (33). In 2014, SmartTots convened a meeting to review the data from animal and human studies and concluded that the current data were sufficiently convincing that prospective randomized controlled clinical trials were warranted to determine whether general anesthetics are potentially neurotoxic (11, 12).

Up to now, several prospective clinical trials designed to provide more definitive data on the effect of anesthetics on brain development in humans are ongoing.

**The GAS (General Anesthesia compared to Spinal Anesthesia) Study (34, 35)**

It’s a prospective, open-label, international, randomized controlled equivalence trial. It recruited 722 infants younger than 60 weeks postmenstrual age, born at greater than 26 weeks’ gestation, and who scheduled for inguinal herniorrhaphy, from 28 hospitals in Australia, Italy, the USA, the UK, Canada, the Netherlands, and New Zealand Between Feb 9, 2007, and Jan 31, 2013. 363 infants were randomly assigned to receive awake-regional anesthesia and 359 to sevoflurane-based general anesthesia. The vast majority of the subjects were male (81% regional, 85% general). The average age at the time of anesthesia was 68.9 days (regional), and 71.1 days (general). The average sevoflurane exposure time was 54 min. The primary outcome of the trial was the Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III) Full Scale Intelligence Quotient score at age 5 years. The secondary outcomes were the postoperative apnea and composite cognitive score of the Bayley Scales of Infant and Toddler Development III (Bayley-III) at 2 years old.

The preliminary results reported the secondary outcomes have been published in 2015 (35) and 2016 (34) showed that an exposure to sevoflurane of less than 1 hour does not increase the incidence of apnea or lower the cognitive composite score compared with regional anesthesia at 2 years of age. The prospective randomized control design of the trial is powerful, so it is almost the strongest clinical evidence to date that brief exposed to sevoflurane in infancy does not result in long-term neurotoxicity. However, longitudinal neurodevelopmental outcome studies have documented that follow-up is important to obtain accurate estimates of neurodevelopmental morbidities. Because cognitive deficits may worsen with age (36, 37) and any neurocognitive problem may only be recognized in older children capable of more complex neuropsychological analysis, we cannot make a final conclusion until the primary endpoint data from this study is published after 2018.

**The PANDA (Pediatric Anesthesia and Neurodevelopment Assessment) Study (38, 39)**

This is a multicentre ambidirectional sibling-matched cohort trial which conducted between May 2009 and April 2015 at 4 university-based US pediatric tertiary care hospitals. The study enrolled 105 biologically related siblings, one of which received inhaled general anesthesia for herniorrhaphy before age of 3 years. At the time of exposure, subjects were on average 1.5 years of age, and were overwhelmingly ASA I. The anesthesia duration ranged from 20 to 240 minutes, with a median duration of 80 minutes. A comprehensive battery of neuropsychological assessments was tested at the ages 8 to 15 years.

The primary outcome was global cognitive function (WASI-IQ score) and the secondary outcomes were domain-specific cognitive functions including memory, learning, motor ability, processing speed, visuospatial ability, attentiveness, executive function, language, and behavior (39). Results showed that mean IQ scores between ex-
posed siblings and unexposed siblings were not statistically significantly different. There was also no significant difference in mean scores of all the secondary outcomes. The authors concluded that among healthy children with a single anesthesia exposure under age 3 does not result in cognitive deficits (38).

The sibling-matched design minimized the influences of genetic background, familial environment, parental education, and other indexes of socioeconomic status, all key factors affecting neurodevelopment. One limitation, however, is that as the families in the study come from a higher socioeconomic status than the general population, and some preclinical studies suggest that enriched environment may reduce the severity of anesthetic effects (40, 41). Further study of repeated exposure, prolonged exposure, and vulnerable subgroups is needed.

The MASK (Mayo Anesthesia Safety in Kids) Study (42)
It concludes 2 interrelated studies, the prospective MASK study and retrospective MASK study. The retrospective study has been listed in table (24), and result similarly to older studies used the same birth cohort (21-23).

The prospective arm included 1000 children in the birth cohort born between 1994 and 2007 in Olmsted County, Minnesota. 500 children had no exposure to general anesthesia prior to the age of 3 years, 300 had single exposure, and 200 had multiple exposures. Subjects from the three groups will undergo prospective testing between the ages of 8 and 12 years or 15 and 19 years during the period 2012-2016. Testing includes the National Center for Toxicological Research- Operant Test Battery (NCTR-OTB), a neurodevelopmental test that can also be used with nonhuman primates, and other neuropsychological tests for cognition, memory, language, executive function, motor and visual spatial tasks, attention, and processing speed with the goal of finding a phenotype for anesthetic neurotoxicity. This research has also collected data on the anesthetic agents used, in addition to intraoperative physiological data such as maximum and minimum blood pressure and oxygen saturation and will include these parameters in their final analysis.

Now, the research is still pending further analysis and will be completed by the end of 2016. Based on previous observation studies the authors hypothesize that multiple, but not single, exposure(s) to general anesthesia will be associated with impairment in multiple domains of the neuropsychological assessment battery, and that domains related to learning and intellectual ability will be affected, whereas those related to memory may not be.

The MASK study will provide a detailed phenotype of anesthetic-associated outcomes. More importantly, it is the first prospective study includes repeated exposures group, which may fill the blank of data regarding longer duration anesthetic exposure.

Conclusion and Practical Advice
Different types of studies rely on each other to move science forward. Most well-conducted clinical trials including PANDA and GAS suggested encouraging results that there is no significant neurocognitive deficit for single or brief anesthetic exposure early in life. However, there are several major considerations to keep in mind. First, all the current studies have limitations. The GAS trial has yet to release the primary endpoint, IQ testing at age 5, and the PANDA trial may not represent the general population given the high socioeconomic status and high control IQ scores. So far the data were too insufficient to draw firm conclusions. Second, some observational studies found that multiple or longer duration anesthetic exposures (>120 min) was a significant independent risk factor for neurodevelopment. Third, no defined critical age at exposure has been widely recognized. Most studies enrolled children exposed to anesthesia before 3-4 years old, but a study found out that children initially exposed to anesthesia over age 3 had an increased risk of motor deficit, indicating that there may be distinct windows of vulnerability for different neurodevelopmental domains in children (29). The results from all these studies will be important for guiding the design of future clinical trials.

In conclusion, a majority of well-designed studies provide some reassurance regarding single or brief anesthetic exposure on immature hu-
man brain, but many questions surrounding early anesthesia and cognition remain unanswered. So far, surgeons, anesthesiologists and parents should be careful, as far as possible to reduce the time and duration of children exposed to anesthesia. Elective surgeries should be delayed for more than 3 years of age.

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References


