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Behavior and Development in Children and Age at the Time of First Anesthetic Exposure

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Background: **Several experimental studies have suggested that early exposure to anesthetic agents, *i.e.*, before completion of synaptogenesis, can result in widespread apoptotic neuronal degeneration and late cognitive impairment, but human data are lacking. The authors performed a retrospective pilot study to test the feasibility and calculate sample sizes for a larger epidemiologic study of disturbed neurobehavioral development as a function of age at the time of first anesthetic exposure. Pediatric urological procedures were selected because the timing of surgery depends mainly on the age at which a diagnosis is made.**

Methods: **Neurobehavioral development was assessed using the validated 120-item parental Child Behavior CheckList/4–18 in 314 children who were operated for pediatric urological procedures between the ages of 0 and 6 yr.**

Results: **Of 243 questionnaires returned, the total problem score was clinically deviant in 41 (23%) of children aged less than 24 months at the time of first surgery and 13 (20%) aged greater than 24 months. Crude and adjusted odds ratios for a clinically deviant Child Behavior CheckList/4–18 score increased with younger age at the time of surgery, but the confidence intervals were very wide. Adjusted odds ratio was 1.38 (0.59–3.22) when operated at age less than 6 months, 1.19 (0.45–3.18) when operated between 6 and 12 months of age, and 1.20 (0.45–3.20) when operated between 12 and 24 months (using operated at greater than 24 months of age as reference category). A properly powered cohort study would require at least 2,268 children.**

Conclusions: **Children undergoing urologic surgery at age less than 24 months showed more behavioral disturbances than children in whom surgery was performed after age 2 yr, although the results were not statistically significant. To confirm or refute an effect of anesthesia on cognitive development, at least 2,268 children need to be studied. With retrospective study designs, residual confounding remains an issue that can only be solved in prospective randomized studies.**

SEVERAL experimental studies have suggested that early exposure to anesthetic agents *i.e.*, before completion of synaptogenesis, can result in widespread apoptotic neuronal degeneration and late cognitive impairment.[1–6] Much debate is going on regarding the influence of timing of exposure to anesthetics (window of vulnerability) and the possibility of a dose-response relationship.[7] Initial data were limited to rodents, in which a clear window of vulnerability appears to exist within the first days after birth. However, rodents are born at a much less developed stage of maturity than primates.[8] Slikker *et al.* recently found that ketamine administered to rhesus monkeys at gestational day 122 or at day 5 or 35 after birth may cause neuronal cell death that was "age" (developmental stage)–dependent.[9] The vulnerability window was within the first week of life; 24-h exposure to ketamine at day 35 did not result in demonstrable neuronal loss. Although 24-h ketamine infusions resulted in significant increases in the number of caspase 3–, Fluoro-Jade C–, and silver stain–positive cells in the frontal cortex of postnatal day 5 monkeys, 3-h exposures did not. This suggests that apart from the vulnerability window there could also be a dose-response relationship (*i.e.*, deeper levels of anesthesia would be more harmful) or a threshold phenomenon in which duration of anesthetic exposure needs to exceed a particular duration before a clinical effect becomes detectable.

If, given a particular set of conditions (patient age, duration of anesthesia, and perhaps dose), anesthetic exposure in human neonates and/or infants could produce sufficient neurodegeneration to result in disturbed neurobehavioral development, the consequences for pediatric surgery and pediatric anesthesia would be considerable. In each case in which surgery is indicated, clinicians and parents would need to weigh the risk of exposure of the infant to anesthesia against the possibilities and risks of postponing surgery. Although several authors have argued that human data are urgently needed, clinical studies are scarce.[10] Various studies have reported short-term alterations in cognitive abilities and behavior after surgery and anesthesia in young children (see Loepke *et al.*[11] for an overview). Long-term neurocognitive impairment has been investigated in specific patient groups such as critically ill neonates, young children undergoing congenital cardiac surgery, and children with prenatal exposure to anesthetics. However, larger studies focusing on the influence of anesthetic exposure at an early age on later cognitive development are lacking.[11]

In this epidemiologic study, we focused on the relationship between age at the time of first anesthetic exposure and disturbed behavioral development at least 4 yr after surgery, hypothesizing that children who underwent anesthesia at a younger age show more deviant

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behavior. We have chosen the domain of pediatric urological procedures because in this area many solitary urogenital anomalies exist unaccompanied by general illness. Furthermore, the timing of surgery in many cases depends mainly on the age at which a diagnosis is made, and postponing the procedure can be an option in selected cases. The results of this initial study are used to determine the feasibility and the required number of patients of a large-scale study.

Materials and Methods

This retrospective cohort study included children undergoing pediatric urological surgery in the years 1987, 1991, 1993, and 1995 in the academic pediatric hospital of the University Medical Center Utrecht. Individuals in the cohort were between ages 0 and 6 yr at the time of surgery. Surgery was predominantly done for obstructive uropathy like ureteropelvic junction obstruction, obstructive megaureter, or posterior urethral valves. Hypospadias surgery was routinely planned at 12–14 months of age. All children were operated by one of the two Pediatric Urologic surgeons.

The anesthetic techniques used in the years studied were predominantly inhalation-based and consisted of mask induction with a volatile agent (halothane, enflurane, or isoflurane) combined with nitrous oxide and an opioid (fentanyl or sufentanil). Total intravenous anesthesia with propofol and an opioid was rarely used. For selected procedures, general anesthesia was sometimes supplemented with a caudal epidural block.

On the basis of records kept by the Pediatric Urologic surgeons, the hospital database was queried for medical history to determine initial eligibility. If the patients met one of the following exclusion criteria, parents were not contacted: presence of congenital diseases other than the (congenital) malformation requiring the urological surgery (*e.g.*, spina bifida, congenital heart surgery, congenital psychomotor retardation), other events in medical history that are known or suspected to be related to later cognitive impairment (*e.g.*, peripartum cerebral ischemia, hypoxic brain injury, or metabolic events; having been ventilated in a neonatal Intensive Care Unit; malignancies), or procedure-related criteria (*e.g.*, urgent surgery, day-care surgery). Children currently living outside the Netherlands and children who have been adopted were also excluded from the analysis, as were children older than 19 yr at the time of contacting the parents. The complete set of exclusion criteria is presented in table 1.

Parents of potentially eligible children received a letter explaining the purpose of the study and its methods and were asked to consider participation. A week later, they were contacted by telephone (MN or MB) to answer any possible remaining questions regarding the study. If the parents indicated that they were willing to participate, they were sent questionnaires by mail along with a consent form to be completed and signed and an addressed stamped return envelope. The Institutional Review Board of the University Medical Center Utrecht, The Netherlands, approved the study protocol.

Table 1. Exclusion Criteria

- Other congenital diseases
  - Congenital syndromes
  - Spina bifida
  - Congenital heart surgery
  - Osteogenesis imperfecta
  - Sickle cell anemia
  - Cystic fibrosis
  - Congenital psychomotor retardation
- Events in medical history possibly related to cognitive impairment
  - Documented peripartum cerebral ischemia/hypoxic brain injury
  - Peripartum metabolic events (hypoglycemia, infection, seizures)
  - Having been ventilated in a neonatal Intensive care Unit
  - Kidney transplantation or dialysis
  - Received high doses of corticosteroids
  - Malignancies
  - Documented disturbed liver function
  - More than three comorbidities
- Procedure-related
  - Urgent operation because of hydronephrosis with uremia
  - Any urological procedure performed in day surgery
- Other
  - Currently living outside the Netherlands
  - Children who have been adopted
  - Aged > 19 years at moment of questionnaire

Age of First Exposure to Anesthetics

The age of the patient at first anesthetic exposure was calculated on the basis of the hospital charts. Subsequently, patients were divided into categories to distinguish between patients exposed to anesthetics within the window of vulnerability and after this period. Traditionally, the age of 2 yr was considered the upper limit for the window of vulnerability in humans.[12] Therefore we have divided patients into two groups: first exposure to anesthesia before and after 24 months of age. Furthermore, as more recent techniques have indicated that the brain growth spurt in humans may occur much earlier, even in the prenatal phase,[1,13] we also divided patients into four categories: first exposure to anesthetics at 0–6 months, 6–12 months, 12–24 months, and greater than 24 months of age.

Behavioral Development

To measure possibly disturbed behavioral development, the Dutch translation of the Child Behavior Checklist/4–18 (CBCL/4–18), developed and validated in the United States,[14] was used. The CBCL/4-18 is to be completed by the parent or a parent surrogate and tests the parent's report of their child's competencies and behavioral/emotional problems based on the child's activities, social relations, and school performance. The parent provides information on 20 competence items and rates the child on 120 problem items using a 3-point scale (0 = not true, 1 = somewhat or sometimes true, 2 = very true or often true) on behaviors in the past 6 months. Examples of statements that are to be rated are "the child feels worthless/inferior" and "the child is inattentive or easily distracted."** For the current analysis only the part of the questionnaire related to behavioral problems was used.

The scores for internalizing problems, externalizing problems, and the total problem score were calculated according to the manuals.[14,15] In accordance with the manual, missing values in the 120-items were replaced by zeroes unless missing values occurred on more than eight items, in which situation the case was removed from the analyses. Behavior of the children was identified as clinically deviant (yes/no) using the threshold values for the Dutch population,[15] which make a distinction between boys and girls and between the age categories 4–11 and 12–18 yr.

Potential Confounding Variables

This was an observational study on the association between age of first exposure to anesthetics and impaired behavioral development later in life; therefore, several confounding variables could influence the observed association. In a separate questionnaire the parents were asked to provide additional information on the behavior of the child and on potentially influencing variables, notably their level of education (to be entered separately for the mother and father), birth weight of their child, gestational age, and whether problems occurred during birth, whether the child had any congenital disease, whether it had been exposed to trauma, and whether the child had problems at school. The parents were also asked to indicate if, in their opinion, the child's development was in any way unusual or abnormal.

Statistical Analysis

First, we compared the patient characteristics across the two age of first anesthetic exposure categories. We then quantified the association between age at the time of first anesthetic exposure (categorized as either four or two categories) and the occurrence of clinically deviant behavior at later age, using the odds ratio with 95% confidence intervals (CI) for each category with the oldest age group as reference category. We subsequently used multivariable logistic regression analysis to adjust this association for possible confounding.

Missing values occurred in the variables birth weight (6% of the cases) and in the level of education of the father and mother (both 3% missing). As imputing missing values is generally preferred to complete case analysis,[16,17] these missing data were single imputed using a regression model approach with addition of a random error component before conducting the analyses.

All analyses were conducted using SPSS version 14.0 (SPSS Inc, Chicago, IL) and S-PLUS, professional edition, version 6.2 (Insightful Corp, Seattle, WA).

The current study was set up as a pilot study to investigate the feasibility of a large-scale epidemiological study. We finally performed a sample size calculation for such a study to determine the number of patients required to detect a statistically significant effect of the effect size found in the current study, using a level of significance of 0.05 and power of at least 80% (using PASS 2008 software, NCSS, Kaysville, UT).

Results

After initial screening of the hospital records of children operated for pediatric urological procedures between the ages of 0 and 6 yr, 368 patients were found to comply with the inclusion criteria of the study (1987, 15 patients; 1991, 112 patients; 1993, 111 patients; 1995, 130 patients). For 43 patients, the municipal administration of the last known parental address was requested to provide information on the new place of residence; for 34 parents, contact information could not be retrieved. Twenty parents refused to participate after the initial phone call, so questionnaires were sent to the parents of 314 children. A total of 249 questionnaires were returned. When verifying the exclusion criteria, two of these children turned out to be adopted, and one patient was too old at the moment of the CBCL/4–18 questionnaire (19 yr). For 3 patients, more than 8 items on the CBCL/4–18 score were missing (which was a reason to remove them from the analyses according to the manual[15]), rendering 243 patients for the analyses.

Table 2 shows the distribution of the patient characteristics, including potential confounders, in the entire cohort and across the two age of exposure categories. Almost 75% of the patients underwent anesthesia for the first time before the age of 2 yr. The average age at the time of the first anesthetics exposure was 17.0 months (median 11.3). In total 71.1% of the children were operated more than once before the age of 6 yr, this percentage was similar for both age groups. Gestational age was slightly lower in the patients who underwent first anesthesia before 24 months, birth weight was almost similar.

** English version of the CBCL/4-18. Available at: http://www.aseba.org/support/SAMPLES/CBCLSample.pdf. Accessed December 8, 2008.

Table 2. Patient Characteristics and Potential Confounders in the Total Cohort and Across the Two Age Groups

	Entire Cohort	By Age at Time of First Anesthetic < 24 months	By Age at Time of First Anesthetic > 24 months
N	243	178	65
Patient characteristics			
Boys, n (%)	183 (75.3)	144 (80.9)	39 (60.0)
Age at anesthesia, months	11.3 (3.1–25.4)	6.8 (1.4–12.7)	44.0 (31.7–52.0)
Age at questionnaire, yr	14.5 (12.5–15.8)	14.0 (12.1–15.1)	16.5 (14.3–18.2)
More than 1 anesthesia	173 (71)	126 (71)	47 (72)
Twins	8 (3.3)	7 (4.0)	1 (1.5)
Gestational age, weeks	40 (38–41)	39 (37–40)	40 (39–41)
Birth weight, g	3,300 (2,865–3,855)	3,300 (2,845–3,845)	3,310 (3,000–3,850)
Education of mother			
Elementary	34 (14.0)	23 (12.9)	11 (16.9)
Low	73 (30.0)	53 (29.8)	20 (30.8)
Middle	74 (30.5)	58 (32.6)	16 (24.6)
High	62 (25.5)	44 (24.7)	18 (27.7)
Education of father			
Elementary	3 (1.2)	2 (1.1)	1 (1.5)
Low	58 (23.9)	47 (26.4)	11 (16.9)
Middle	87 (35.8)	61 (34.2)	26 (40.0)
High	95 (39.1)	68 (38.2)	27 (41.5)

Values represent medians (interquartile range) for continuous variables and number (%) for categorical variables.

Table 3 describes characteristics of the patients that are possibly related to neurocognitive impairment and the results of the CBCL/4–18 questionnaire. The parents of the children in the younger age group considered more than twice as often their child as having a handicap when compared to the older age group (13.5% *vs.* 6.2%). In total, almost half of the children experienced problems at school, and 30% had to repeat grades at least once. The median total CBCL/4–18 problem score was 18.0, with higher values (indicating more problems) in the patients who underwent anesthesia before 24 months of age: 19.0 *versus* 17.0. This difference was not to be attributed to a specific type of problems (internalizing and externalizing scores did not deviate between the groups). In total, 22.2% of the patients had a clinically deviant CBCL/4–18 total score, with more clinically deviant scores in the patients who were operated before 2 yr of age (23.0% *vs.* 20.0%). This difference results in an odds ratio of 1.20 (95% CI 0.59–2.41) on clinically deviant behavior when comparing patients undergoing their first anesthesia before 24 months with patients who underwent anesthesia after 24 months.

Table 4 shows the crude and adjusted odds ratios when the age of first anesthetic exposure was divided into four categories on having a clinically deviant CBCL/4–18 score at later age. A trend towards increased risk at younger age was present, with and without adjustments, especially in patients operated at very young age (0–6 months). These findings were, however, not statistically significant, as indicated by the wide confidence intervals.

Based on the prevalence of a clinically deviant CBCL/4–18 score of 0.20 in children who underwent pediatric urological surgery after 2 yr of age and of 0.23 if the operation was performed before 2 yr of age, a cohort of 6,020 patients would be needed to confirm or refute this

Table 3. Characteristics of Potential Cognitive Impairment in the Total Cohort and Across the Two Age Groups

	Entire Cohort	By Age at the Time of First Anesthetic < 24 months	By Age at the Time of First Anesthetic > 24 months
n	243	178	65
Handicapped*	28 (11.6)	24 (13.5)	4 (6.2)
Problems at school	117 (48.3)	94 (52.8)	23 (35.9)
Repeat one or more grades	73 (30.0)	51 (28.7)	22 (33.7)
CBCL 4–18			
Total problem score	18.0 (9.0–34.5)	19.0 (10.0–34.8)	17.0 (8.0–31.0)
Internalizing score	5.0 (2.0–11.0)	5.0 (2.0–11.0)	5.0 (2.0–10.0)
Externalizing score	4.0 (1.0–9.0)	4.0 (1.0–8.8)	4.0 (1.0–9.0)
Clinically deviant score†	54 (22.2)	41 (23.0)	13 (20.0)

Values represent medians (interquartile range) for continuous variables and number (%) for categorical variables.

* Parents response to question: "Does your child have a handicap in the area of memory, learning or social behavior?" † Clinically deviant: threshold values for total Child Behavior Checklist/4–18 (CBCL/4–18) problem score according to Dutch norms[15] are: boys 4–11 yr: 40; girls 4–11 yr: 36; all 12–18 yr: 37.

Table 4. Influence of Age at the Time of First Anesthetic Exposure on the Presence of a Clinically Deviant CBCL/4–18 Score

Model	Description	Odds Ratio (95% CI) for Age at Time of First Anesthesia			
		< 6 months	6–12 months	12–24 months	> 24 months
n		84	44	50	65
Crude estimate					
1	Age at first anesthetic exposure	1.33 (0.61–2.92)	1.17 (0.46–2.98)	1.00 (0.40–2.51)	1
Adjustment for potential confounders					
2	Model 1 + gestational age	1.45 (0.65–3.21)	1.22 (0.48–3.09)	1.07 (0.42–2.70)	1
3	Model 2 + birth weight	1.46 (0.66–3.23)	1.22 (0.48–3.10)	1.07 (0.42–2.70)	1
4	Model 3 + more than one anesthetic exposure	1.39 (0.62–3.09)	1.28 (0.50–3.29)	1.17 (0.46–2.99)	1
5	Model 4 + education father	1.31 (0.57–3.01)	1.14 (0.43–3.00)	1.15 (0.44–3.02)	1
6	Model 5 + education mother	1.38 (0.59–3.22)	1.19 (0.45–3.18)	1.20 (0.45–3.20)	1

Patients who underwent their first anesthetic after 24 months of age serve as the reference group. Odds ratios are based on logistic regression modeling. CBCL = Child Behaviour Checklist; CI = confidence interval.

finding with alpha set at 0.05 and beta of 0.80. If we assume that the window of vulnerability in humans does not extend beyond 6 months after normal term birth, a comparison between children who were operated between birth and 6 months of age and children operated after 6 months of age would require 2,268 subjects (assuming prevalences of a clinically deviant CBCL/4–18 score of 0.25 and 0.20 respectively).

Discussion

We have studied child behavior as recorded by parents of children who underwent pediatric urological surgery 11–14 yr earlier and calculated the odds ratios for a clinically deviant score as a function of age at the time of first surgery. More than 90% of the parents of eligible patients could be contacted; of this group, 75% consented to participate and fill in the questionnaires. Hence, on the basis of the results of this initial study and the power calculations derived from these results, we conclude that it is both necessary and feasible to perform a larger-scale cohort study to assess the effect of timing of surgery on cognitive development of children.

The results of the present investigation cannot answer the question whether early as opposed to later pediatric urological surgery is causally related to the risk of a deviant child behavior check list score later in life. The main reason is that we found extremely wide confidence intervals around the point estimates of both the crude and adjusted odds ratios. Nevertheless, there was a trend towards a relationship between age at the time of surgery and the magnitude of the odds for an abnormal CBCL/4–18 score, where the highest odds for a deviant CBCL/4–18 score were found in children who had undergone early surgery (aged 0–6 months). Adjusting for confounders such as gestational age, birth weight, multiple anesthetic exposures, and education of the parents, did not remove this pattern.

The current study was conducted as a pilot-study to verify feasibility of a larger study, and as such has some limitations. First, as indicated above, there is much debate on the 'window of vulnerability' in humans.[1,7] We have taken this uncertainty into account in the current analysis by comparing children undergoing anesthesia before and after 24 months, and also conducted a second analysis in which the categories for age of first anesthetics use were more refined. Also we conducted two sample size calculations, using both the 2 yr and the 6 months age thresholds. In future studies, more extensive methodology should be used to study the influence of age of first anesthetic exposure.

A second discussion in the current literature focuses on whether anesthetic-induced neurodegeneration – if it exists in humans– occurs only when the duration of anesthetic administration has exceeded a threshold below which there will be no clinically detectable long-term effects.[5,7] In the current study, we were unable to take duration of anesthesia into account (because the original anesthesia records were no longer available) and focused on the age at the time of first anesthetic exposure only. If, however, such threshold phenomena indeed are present in humans, this should be included in the analysis and should also be taken into account in the selection of the disease domain. It may, for example, be unwise to initiate a large study in herniotomy patients if the average duration of anesthesia is less than 30 min in the majority of cases, even when the operation is performed at an age that lies within the window of vulnerability.

Third, we cannot exclude that our results might be disturbed by considerable residual confounding, as we could not include information on, for example, major life events. One of the most important confounders may be that the indication for the surgery or the timing of the procedure is not independent of factors that may also influence neurobehavioral development, such as comorbidity. In other words, the decision to operate a child at, for example, 3 months of age could depend on the severity of symptoms resulting from an anatomical anomaly that may also influence neurobehavioral development. We tried to mitigate this problem by focusing on pediatric urological procedures for which timing of surgery depends mainly on the age at which a diagnosis is made.

Finally, we used a clinically deviant CBCL/4–18 problem score to indicate neurodevelopmental impairment. This questionnaire focuses, however, on only one aspect of development, namely problematic behavior as perceived by the parents. In future large-scale studies, more extensive cognitive and behavioral testing will be required.

Therefore, altogether extreme care should be exercised before interpreting the apparent age-response relationship observed in the current study as evidence for clinically relevant anesthetic neurotoxicity in children undergoing pediatric urological surgery before the age of 2 yr. Considerable statistical power will be needed to identify or exclude a causative contribution of anesthesia to a deviant CBCL/4–18 score and to prevent researchers from committing a type II error (erroneously concluding that exposure to anesthesia early in life does not contribute to neurobehavioral disturbance). We aimed to test the feasibility of this approach and to contribute to improving the design of future, adequately powered nationwide epidemiological studies (both retrospective and prospective) by providing the elements for proper power analyses.

When designing a large study to investigate the influence of anesthetic exposure on later cognitive development, several methodological issues are to be considered.

The ideal study design would be a randomized trial, comparing subjects randomized to undergo anesthesia with those not undergoing anesthesia. However, the methodological obstacles for such a study (both in adults and children) are huge. Besides ethical constraints, the main problem is the tight marriage between anesthesia and surgery,[13] which makes it unclear whether potential cognitive impairment is to be attributed to the use of anesthetics or to surgery in itself. Hence, a 2 × 2 factorial design could be ideal from a purely methodological viewpoint, but this as well is clearly unfeasible. It is unethical to ask patients to consent to randomizing their child into a 3 h of anesthesia only group *versus* 3 h of anesthesia + surgery group. Furthermore it is nowadays completely unacceptable to expose pediatric surgical patients to a surgery only group. Although several decades ago, many anesthesiologists argued that the immature neonatal brain was unable to feel pain and, therefore, performed surgery using only nitrous oxide and muscle relaxants without analgesia (the so-called Liverpool technique), this view has now been abandoned on the basis of research showing brain activation and a strong stress response in unanesthetized neonates undergoing surgery without opioid analgesia.[18]

A next best study design would be to randomize pediatric surgical patients undergoing suitable surgical procedures into general anesthesia *versus* regional anesthesia groups. Indeed, such an approach was taken by the ISPOCD study group (International Study of Postoperative Cognitive Decline) to investigate postoperative cognitive dysfunction in middle-aged patients.[19] Remarkably, that study was unable to find any beneficial effect on the incidence of postoperative cognitive decline of avoiding general anesthesia in favor of regional anesthesia. Factors to be considered are that such an approach would restrict the domain to children aged 0–2 yr undergoing subumbilical surgical procedures in which regional anesthesia (spinal, combined spinal/epidural, or caudal) would be a practically feasible alternative to general anesthesia. Infants often tolerate spinal anesthesia well and will sometimes even fall asleep as a result of transient functional deafferentation of the lower body.[20] However, up to 80% of infants undergoing surgery with regional anesthesia may need additional sedation to keep them sufficiently immobile to allow surgery.[21] Obviously, administering benzodiazepines or other GABAergic drugs to infants during regional anesthesia would defeat the entire purpose of this particular study design.

Finally, investigators might decide on a nonrandomized comparison of children undergoing anesthesia and surgery to children who are either not hospitalized (siblings or classmates) or children hospitalized for pediatric medical (nonsurgical) conditions. By definition, this design would not allow the investigators to distinguish between anesthetic-induced *versus* operation-induced behavioral disturbances later in life. Examples of the latter would include the effects of having the surgical condition, hospitalization, the surgery itself with the attendant inflammatory response, as well as the effects of the hospitalization and recovery of the child on the rest of the family, particularly the effects of the child's disease on parents and siblings.[11] In this type of design, confounders are likely to play a major role and should therefore be carefully recorded and analyzed.

To reduce many of the problems occurring in the aforementioned designs, we chose not to compare children with and without anesthesia, but rather to focus on the influence of the age at the time of first anesthetics exposure on later cognitive behavior in children who all undergo general anesthesia.

For this comparison, the ideal design would be a randomized clinical trial comparing subjects randomized to early surgery with late surgery. However, this design requires that surgery can be safely postponed, which is often not the case.

The next best alternative to a randomized clinical trial is a large retrospective epidemiological study, but the

Table 5. Criteria for Causality[23] Applied to the Possible Association between Clinical Exposure to Anesthetics and Occurrence of Deviant Behavioral Scores

Causal Principle	Validity	Comment
Strength of the association	±	Association not yet shown in humans; in experimental studies, there is both a dose response and window of vulnerability corresponding to the peak in synaptogenesis.
Consistency	±	No clinical studies yet; not all experimental studies support the evidence for anesthetic-induced apoptotic neurodegeneration.
Specificity	±	Not very strong; there are multiple causal pathways to disturbed neurobehavioral development; there are multiple potential confounders (most of which are not routinely recorded in hospital charts).
Temporality	++	The window of vulnerability is a strong indicator of temporality.
Biological gradient	++	In neonatal experimental animals, the association between exposure to anesthetics in clinical concentrations and neurodegeneration is clearly dose-dependent.
Plausibility	++	Lack of synaptic input is a known trigger for (physiological) neurodegeneration in the developing brain. Anesthetic-induced deafferentation of sufficient duration could be a plausible mechanism for apoptotic neurodegeneration during critical periods of brain development (brain 'growth spurt'). Direct neurotoxic effects might explain immediate (necrotic) cell death.
Coherence	–	Experimental evidence fairly coherent. Clinical coherence remains unknown until more clinical studies – of different designs – will become available.
Experiment	+++/+	Rodent – and recently primate – experiments consistently show apoptotic neurodegeneration. There is much evidence for cell death and neurodegeneration; evidence for behavioral effects is growing. These studies are the main source of data for the clinical suspicion that anesthetic exposure of young children could result in clinically manifest developmental disturbances.
Analogy	+	Fetal alcohol syndrome.

greatest challenge is to obtain complete documentation of all potential confounders to allow for proper adjustment in the statistical analysis.[22] In everyday clinical practice, many potentially relevant confounders will not have been routinely documented in the hospital chart.

Altogether, to obtain more insight in the influence of anesthesia at a young age on later cognitive development, both retrospective and prospective studies are required, and the results can be combined subsequently by means of triangulation.

In 1965, the famous pioneer epidemiologist Sir Austin Bradford Hill, Ph.D., F.R.S. (1897–1991; president of the Royal Statistical Society 1950–1952) suggested nine criteria that an investigator might use when attempting to distinguish between association and causation: strength of the association, consistency, specificity, temporality, biologic gradient, plausibility, coherence, experiment, and analogy.[23] None of these criteria can bring "indisputable evidence for or against the cause and-effect hypothesis," neither is any criterion—except the criterion of temporality[24]—a necessary requirement for causation. In table 5, however, we do summarize the available evidence for clinically relevant anesthetic neurotoxicity in terms Hill's criteria of causation. The lack of human data are the main reason that coherence and consistency are still limited. Larger human studies are urgently needed, but the best prospective study designs are unethical (if randomized) or take a considerable time to complete (a minimum of 4 yr between inclusion of infants and the ability to reliably diagnose neurobehavioral abnormalities) before providing answers that may be translated into meaningful advice to clinicians and parents.

In conclusion, we have assessed the feasibility of retrospectively studying the relationship between age at the time of first exposure to general anesthesia and the presence of "deviant" neurobehavioral scores as determined with a validated parental questionnaire. This design appears feasible, and the sample size requirements for an adequately powered study range from 2,268 to 6,020, dependent on the age groups that are being compared. Given these numbers, large-scale collaboration is required for a future study, which was also recognized by McGowan and Davis as one of the key issues to further understand anesthetic-related neurotoxicity in humans.[7] The unbreakable association between surgery and anesthesia will be a limitation in all study designs, both retrospective and prospective.

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ANESTHESIOLOGY REFLECTIONS

Emerson Respirator or "Iron Lung"

A descendant of Ralph Waldo Emerson, John Haven "Jack" Emerson (1906–1997) demonstrated his mechanical genius by inventing in 1931 the first efficient, economical "iron lung," which he called his "Respirator." When Harvard University sued him for patent infringement, Emerson invalidated Harvard's patents by proving others had prior claims on the tank respirator. "Not bad," Jack noted drily, "for a high school dropout." Unlike his prevailing sense of humor, Emerson's eyes were rarely dry around photographs from the 1950s of school gymnasiums filled with tank-bound polio-stricken children. Many of these youngsters would eventually recover from their suffocating paralysis, courtesy of their tiny versions of his Emerson Respirator. (Copyright © the American Society of Anesthesiologists, Inc. This image appears in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

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