Attention-Deficit/Hyperactivity Disorder After Early Exposure to Procedures Requiring General Anesthesia

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Abstract

Objective: To study the association between exposure to procedures performed under general anesthesia before age 2 years and development of attention-deficit/hyperactivity disorder (ADHD).

Patients and Methods: Study patients included all children born between January 1, 1976, and December 31, 1982, in Rochester, MN, who remained in Rochester after age 5. Cases of ADHD diagnosed before age 19 years were identified by applying stringent research criteria. Cox proportional hazards regression assessed exposure to procedures requiring general anesthesia (none, 1, 2 or more) as a predictor of ADHD using a stratified analysis with strata based on a propensity score including comorbid health conditions.

Results: Among the 5357 children analyzed, 341 ADHD cases were identified (estimated cumulative incidence, 7.6%; 95% confidence interval [CI], 6.8%-8.4%). For children with no postnatal exposure to procedures requiring anesthesia before the age of 2 years, the cumulative incidence of ADHD at age 19 years was 7.3% (95% CI, 6.5%-8.1%). For single and 2 or more exposures, the estimates were 10.7% (95% CI, 6.8%-14.4%) and 17.9% (95% CI, 7.2%-27.4%), respectively. After adjusting for gestational age, sex, birth weight, and comorbid health conditions, exposure to multiple (hazard ratio, 1.95; 95% CI, 1.03-3.71), but not single (hazard ratio,1.18; 95% CI, 0.79-1.77), procedures requiring general anesthesia was associated with an increased risk for ADHD.

Conclusion: Children repeatedly exposed to procedures requiring general anesthesia before age 2 years are at increased risk for the later development of ADHD even after adjusting for comorbidities.

 Mayo Clin Proc. 2012;87(2):120-129

For editorial comment, see page 110

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Exposure of the developing brains of animals to anesthetics and sedatives causes neurodegenerative changes.[1,2] Implicated drugs include *N*-methyl-D-aspartate glutamate receptor antagonists and γ-aminobutyric acid agonists.[2] When administered to young animals, including primates, in doses and durations that approximate those employed in clinical anesthetic care, these drugs cause apoptotic neurodegeneration affecting primarily cortical regions (depending on drug and species).[3] These changes are associated with behavioral deficits in both rodents and nonhuman primates, with deficits noted in learning, attentiveness, and other aspects of behavior.[2-4]

The clinical significance of these observations remains unclear, and it is difficult to predict the expected phenotype of anesthesia-induced injury in humans based on preclinical work. The relatively few extant human studies seeking evidence of anesthesia-induced injury have examined several outcomes, including medical record diagnostic codes possibly related to learning problems, group-administered measures of academic achievement, and learning disabilities (LD).[5,6] Using the last-mentioned approach, our group found an association between multiple, but not single, exposures to procedures requiring anesthesia and subsequent LD in children in a population-based birth cohort, with multiple exposures associated with an approximate 2-fold increase in the incidence of LD.[7,8] Although LD is a reasonable outcome to seek on the basis of the preclinical findings,[2] others are also plausible. For example, neonatal exposure of rodents to *N*-methyl-D-aspartate antagonists produces neural injury associated with hyperactivity that can be ameliorated by dextroamphetamine and indeed has been proposed as a model for human attention-deficit/hyperactivity disorder (ADHD).[9] Children with ADHD exhibit inattention, impulsivity, and motor restlessness, a clinical presentation consistent with a neuropsychological disorder (ie, cerebral dysfunction from a physical cause).[10] The cause(s) of ADHD symptoms are not known, but current theories emphasize the role of executive dysfunction such as behavioral disinhibition.[11] Although ADHD is a heritable disorder, a gene-environment interaction may be important for its clinical expression.[12]

The current study examined the association between exposure to surgery or other procedures (eg, diagnostic procedures) requiring general anesthesia before age 2 years and ADHD in the same birth cohort that we previously used to examine LD as the outcome.[7] This cohort has supported several prior investigations of the epidemiology of ADHD,[13,14] such that rigorous ascertainment of ADHD by well-defined research criteria is available.[14,15] We hypothesized that exposure to multiple, but not single, procedures requiring general anesthesia would be associated with risk for ADHD, similar to our previous findings for LD.[7]

PATIENTS AND METHODS

This study was approved by the Mayo Clinic and Olmsted Medical Center institutional review boards.

Birth Cohort

A previously described cohort of children born in Rochester, MN,[7,13,14] was constructed including all children (N=8548) born between January 1, 1976, and December 31, 1982, to mothers residing in the townships comprising Independent School District No. 535. Children who emigrated or died before age 5 years (n=2830), were severely intellectually disabled (n=19, full-range IQ less than 50 or neurodevelopmentally unable to test), or did not provide authorization to use their medical records in research (n=342) were excluded. The final cohort analyzed thus consisted of 5357 children.[7] These children were observed retrospectively from birth until the initial occurrence of emigration, high school graduation, or death.[13,14,16]

Identification of ADHD Incident Cases

The strategy for identifying ADHD cases has been described in detail previously.[13,14] To summarize, school records of the cohort were searched for any indication of concern regarding learning and behavior. Such concerns include any referral for assessment of a school problem, medical reports, medication records, the presence of an individualized education program (IEP),[8] or any remarks by teachers related to a school problem. Schools in Minnesota and throughout the United States are required to provide an IEP to those who qualify for special education due to LD (cognitive, language, sensory, and physical impairments) and emotional or behavioral dysfunction (EBD). Children requiring IEP-EBD services tend to exhibit more severe forms of disruptive behaviors, and children who have more subtle emotional or behavioral problems may not be deemed eligible to receive these particular services.

Identification of ADHD cases consisted of applying ADHD research criteria to the children with identified concerns.[13,14] The exclusion criteria specified in the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) (DSM-IV)[10] were followed (ie, ADHD was not present if they had a diagnosis of a psychotic disorder, severe mental retardation, or pervasive developmental disorder). Patients were defined as having research-identified "definite" ADHD if their records included a clinical diagnosis of ADHD and at least 1 form of supporting evidence, including documentation of symptoms that met DSM-IV criteria for ADHD (with 6 or more separate entries in the medical or school records that were consistent with DSM-IV criteria) and positive parent or teacher ADHD questionnaire results.

Identification of Cohort Members Exposed to Surgery or Other Procedures Requiring General Anesthesia

All children who underwent any type of surgery or other procedure requiring general anesthesia before their second birthday were identified. For these children, the duration of anesthesia(s), the anesthetic agents used (inhalation, intravenous, sedatives), types of surgery or procedure, number of anesthetic exposures before age 2 years, and age(s) at which exposure(s) occurred were abstracted. Cohort members who were delivered via cesarean section under general or regional anesthesia, as well as those who received regional techniques for labor analgesia, were also identified.

Assessment of Health Status

Health status was quantified using the Johns Hopkins Adjusted Clinical Groups (ACG) Case-Mix System,[17] as previously described.[8] This method, originally designed for children, has been used in a variety of settings to predict costs, utilization, mortality, and morbidity in large populations.[18] The ACG Case-Mix System utilizes the *International Classification of Diseases, Ninth Revision* (ICD-9) diagnosis codes. Codes for each child were converted to ICD-9 and assigned to one of 32 unique morbidity clusters designated as aggregated diagnostic groups (ADG) based on 5 clinical criteria: expected need for specialty care (medical vs surgical), duration of condition (acute, recurrent, or chronic), severity of condition (major and unstable vs minor and stable), diagnostic certainty (symptoms vs documented disease), and etiology of condition (infection, injury, or other).

Statistical Analyses

Each child was considered at risk from birth until meeting diagnostic criteria for ADHD. Cumulative incidence rates were calculated according to the method of Kaplan and Meier with data censored at the initial occurrence of emigration, death, last follow-up date, or age 19 years. Proportional hazards regression assessed whether exposure to procedures requiring general anesthesia (no exposure, 1, or 2 or more exposures) was a risk factor for ADHD. Supplemental analyses were also performed with exposure quantified as the cumulative duration of anesthesia experienced before age 2 years (treated as both a continuous variable and a categorical variable using 30-minute intervals). Both unadjusted and adjusted analyses were performed. An initial covariate-adjusted analysis was performed using proportional hazards regression with covariates including gestational age, sex, and birth weight. To further account for potential differences in comorbid health conditions between patients who received anesthesia before age 2 vs those who did not, a stratified proportional hazards regression analysis was performed with strata defined based on a propensity score. Propensity scores were obtained for each individual using a multiple logistic regression model with exposure to procedures requiring anesthesia before age 2 as the dependent variable. Explanatory variables for this model included birth and maternal characteristics as well as binary indicator variables for each of the John Hopkins ADG morbidity clusters. Children not exposed to anesthesia who had a propensity score lower than the lowest score among those who were exposed to anesthesia were excluded from subsequent propensity-stratified analyses, as were children who were exposed to anesthesia and had a propensity score higher than the highest propensity score among those not exposed to anesthesia.[19] The remaining individuals were divided into 5 strata based on quintiles of the propensity scores. Cochran-Mantel-Haenszel statistics and linear models were used to verify that birth, maternal, and morbidity characteristics were similar between those exposed to anesthesia and those who were not after adjusting for propensity strata. Additional analyses were also performed to assess whether mode of delivery was associated with subsequent development of ADHD, after controlling for postnatal exposure to anesthesia and procedures.

In all cases, separate models were used to evaluate the different exposure variables, with results summarized using hazard ratio (HR) estimates and corresponding 95% confidence intervals (CIs). Analyses were performed using SAS statistical software, version 9.2 (SAS Institute, Cary, NC).

RESULTS

A total of 341 ADHD cases occurring before age 19 years were identified among the 5357 children analyzed (estimated cumulative incidence, 7.6%; 95% CI, 6.8%-8.4%). Patients fulfilled research criteria for ADHD at a mean age of 10.3 years.

Postnatal Anesthesia Exposure

Among the 5357 children, 350 underwent 1 or more procedures (497 total procedures) requiring general anesthesia before age 2 years (not including exposure to general anesthesia during cesarean delivery), with a mean ± SD duration of anesthesia exposure of 133±238 minutes (median, 75 minutes; interquartile range, 45-115 minutes). Of these 350 children, 286 were exposed to general anesthesia once and 64 were exposed 2 or more times. The most frequent anesthetic was a combination of halothane (87.1%) and nitrous oxide (88.1%). Compared with unexposed children, those receiving anesthesia for procedures before age 2 years were more likely to be male, have lower birth weight ($P<.001$), and have lower gestational age ($P<.001$) (Table 1). Those receiving anesthesia for procedures also had more comorbidities as reflected by the ADG cluster frequencies (Table 2).

For children not receiving anesthesia for procedures before age 2, the cumulative incidence of ADHD at age 19 was 7.3% (95% CI, 6.5%-8.1%). For single and multiple (≥2) exposures to anesthesia for procedures, the estimates were 10.7% (95% CI, 6.8%-14.4%) and 17.9% (95% CI, 7.2%-27.4%), respectively (Figure). In unadjusted analysis, exposure significantly increased ADHD risk (Table 3). In analysis adjusted for the covariates of sex, birth weight, and gestational age, multiple (HR, 2.49; 95% CI, 1.32-4.71), but not single (HR, 1.35; 95% CI, 0.90-2.02), exposures to anesthetics for procedures increased ADHD risk. Similar results were found using stratified proportional hazards regression with strata defined based on the propensity for receiving anesthesia (multiple exposure HR, 1.95; 95% CI, 1.03-3.71; single exposure HR, 1.18; 95% CI, 0.79-1.77). When analyzed either as a continuous or a categorical variable, the total duration of anesthesia was also associated with ADHD in unadjusted and covariate-adjusted analysis, but this association did not reach statistical significance in propensity-stratified analysis (Table 3).

In the birth cohort, 932 individuals met criteria for LD before age 19 years. Of the 341 children with ADHD, 240 (70.4%) also met criteria for LD, and 101 children were diagnosed with only ADHD (ie, ADHD without LD). To determine the association between exposure to anesthesia for procedures and ADHD without LD, an additional set of analyses was performed with all children with a diagnosis of LD

TABLE 1. Birth and Maternal Characteristics in the Olmsted County Birth Cohort

	No procedure (N=5007)		Procedure with anesthesia (N=350)		
Characteristic	No. of patients[a]	Summary statistics[b]	No. of patients[a]	Summary statistics[b]	*P* value[c]
Sex	5007		350		<.001
Female		2453 (49.0)		111 (31.7)	
Male		2554 (51.0)		239 (68.3)	
Birth weight (g)	4998	3473±535	350	3396±690	<.001
<2500		198 (4.0)		30 (8.6)	
≥2500		4800 (96.0)		320 (91.4)	
Gestational age (wk)	4692	40.0±2.0	333	39.7±2.7	<.001
<32		29 (0.6)		13 (3.9)	
32-36		277 (5.9)		18 (5.4)	
≥37		4386 (93.5)		302 (90.7)	
Mother's education	4576		316		.433
<12 y		299 (6.5)		16 (5.1)	
12 y		1558 (34.1)		116 (36.7)	
>12 y		2719 (59.4)		184 (58.2)	
Mother's age (y)	5007	26.5±4.7	350	26.9±4.8	.116

[a] Number with information available for the given characteristic.
[b] Data are presented as No. (percentage) of patients or mean ± SD.
[c] Mother's age was compared between groups using the *t* test, and other characteristics were treated as nominal variables and compared between groups using the χ^2 test.

excluded. In this subset of the cohort, the distribution of birth and maternal characteristics and comorbidities among exposed and unexposed children remained similar to that of the full cohort (eTables 1A and 2A, available online at http://www.mayoclinicproceedings.org). Multiple, but not single, exposures to anesthesia for procedures were associated with the risk of ADHD without LD (Table 4). The total duration of anesthesia was not associated with ADHD in this analysis, which may reflect a lack of statistical power given the lower number of children with only ADHD.

Exposure to Anesthesia and Mode of Delivery

In an analysis of the 5180 children in whom data on exposure to anesthesia and mode of delivery were available (full information regarding the mode of delivery was not available or maternal authorization for use of delivery records was denied for 177 children), 497 children were delivered via cesarean section (193 with general anesthesia and 304 with neuraxial block), 1495 children were delivered vaginally with neuraxial block (1274 epidural blocks and 221 spinal blocks), and 3188 children were delivered vaginally without neuraxial blocks. After adjusting for sex, birth weight, gestational age, and number of postnatal exposures to procedures requiring general anesthesia before the age of 2 years, the mode of delivery was not associated with the subsequent development of ADHD (vaginal delivery with neuraxial block: HR,1.26; 95% CI, 0.98-1.62; cesarean delivery with neuraxial block: HR, 1.30; 95% CI, 0.84-2.01; and cesarean delivery with general anesthesia: HR, 1.31; 95% CI, 0.74-2.31, all compared with vaginal delivery without neuraxial block).

DISCUSSION

The results of this study support the hypothesis that, similar to the pattern of our results previously observed for LD,[7,8] multiple, but not single, exposures to procedures requiring general anesthesia during the first 2 years of life are associated with an increased incidence of ADHD.

The clinical diagnosis of ADHD is made on the basis of symptoms of impulsivity, inattention, and motor restlessness that are not developmentally appropriate and using other criteria specified in DSM-IV.[10] Children with ADHD typically exhibit deficits in vigilance, verbal learning, working memory, and measures of executive function.[20] They frequently have comorbid mood, anxiety, or learning disorders, but neuropsychological abnormalities are present independent of such comorbidities.[21,22] For this study, we used research criteria for identification of ADHD incident cases in a population-based

TABLE 2. The Johns Hopkins Adjusted Clinical Groups (ACG) Case-Mix System Scores of Olmsted County Birth Cohort[a]

Variable	No procedure/anesthesia (N=4944)	Procedure with anesthesia (N=348)	*P* value[b]
Time limited: minor	2407 (49)	206 (59)	<.001
Time limited: minor-primary infections	4208 (85)	308 (89)	.084
Time limited: major	573 (12)	104 (30)	<.001
Time limited: major-primary infections	810 (16)	100 (29)	<.001
Allergies	400 (8)	43 (12)	.005
Asthma	406 (8)	30 (9)	.789
Likely to recur: discrete	507 (10)	54 (16)	.002
Likely to recur: discrete-infections	3975 (80)	310 (89)	<.001
Likely to recur: progressive	10 (0.2)	1 (0.3)	.736
Chronic medical: stable	401 (8)	64 (18)	<.001
Chronic medical: unstable	520 (11)	60 (17)	<.001
Chronic specialty: stable-orthopedic	123 (2)	16 (5)	.017
Chronic specialty: stable-ear, nose, throat	53 (1)	10 (3)	.003
Chronic specialty: stable-eye	1181 (24)	114 (33)	<.001
Chronic specialty: unstable-orthopedic	0 (0)	0 (0)	
Chronic specialty: unstable-ear, nose, throat	1 (0.02)	0 (0)	.791
Chronic specialty: unstable-eye	102 (2)	38 (11)	<.001
Dermatologic	774 (16)	73 (21)	.009
Injuries/adverse effects: minor	2056 (42)	175 (50)	.001
Injuries/adverse effects: major	1233 (25)	122 (35)	<.001
Psychosocial: time limited, minor	140 (3)	21 (6)	<.001
Psychosocial: persistent/recurrent, stable	298 (6)	51 (15)	<.001
Psychosocial: persistent/recurrent, unstable	0 (0)	0 (0)	
Signs/symptoms: minor	1589 (32)	146 (42)	<.001
Signs/symptoms: uncertain	899 (18)	89 (26)	<.001
Signs/symptoms: major	1153 (23)	127 (36)	<.001
Discretionary	2511 (51)	274 (79)	<.001
See and reassure	165 (3)	28 (8)	<.001
Prevention/administrative	4846 (98)	347 (99.7)	.024
Malignancy	12 (0.2)	1 (0.3)	.871
Pregnancy	0 (0)	0 (0)	
Dental	196 (4)	17 (5)	.398

[a] Data presented as No. (percentage) of patients. Aggregated diagnostic groups information (see Methods) could not be ascertained for 63 of the 5007 children who did not receive anesthesia and for 2 of the 350 who were exposed to anesthetic.
[b] χ^2 test.

cohort, a concept well established in epidemiology and clinical research.[13,14]

The etiology of ADHD is unknown, but evidence suggests a neuropsychological disorder, with anatomic correlates reported in imaging studies.[23] Family, twin, and adoption studies suggest an important genetic component, and molecular genetic studies suggest several candidate genes, such as those associated with dopamine receptors and transport.[12,24] Environmental factors are also associated with ADHD, suggesting that gene-environment interactions are also operative.[12] Implicated environmental factors include maternal smoking, prenatal alcohol exposure, viral infections, nutritional deficiencies, low parental education level, perinatal stress, and others.[25,26] Many children with ADHD also have a LD, which is characterized by a discrepancy between intellectual capacity and performance on tasks related to reading, language, and written skills.[20,27] Rates of overlap vary depending on how

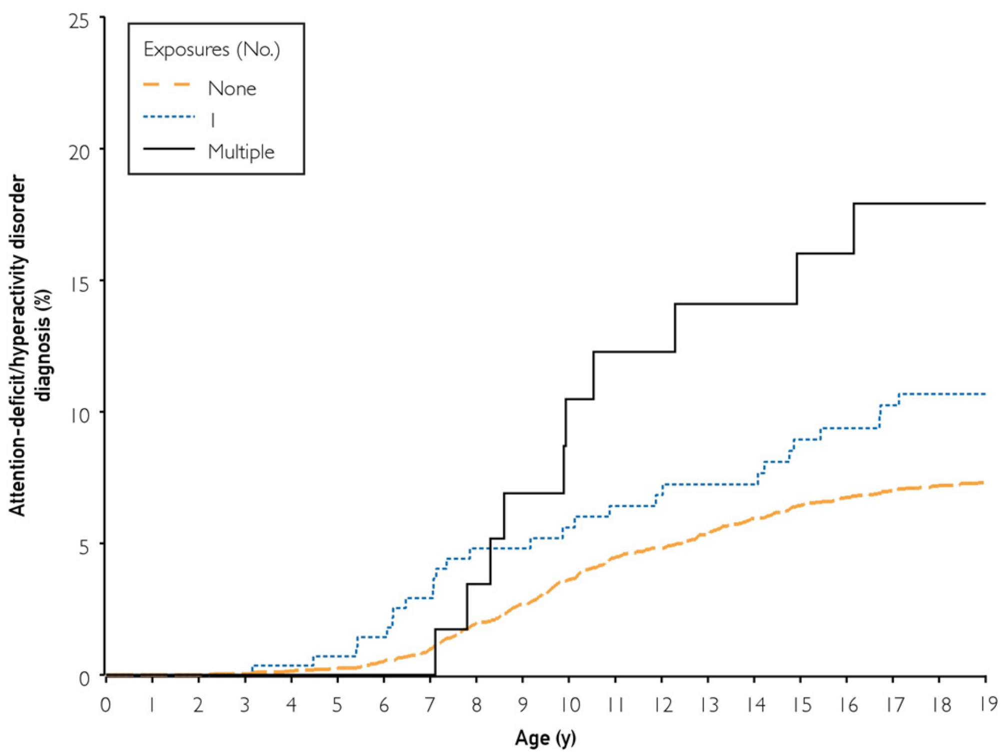

FIGURE. Cumulative percentage of attention-deficit/hyperactivity disorder diagnosis by age shown separately for those that had 0, 1, or multiple procedures performed with general anesthesia under the age of 2 years. The number of individuals at risk at 5, 10, and 15 years of age is 4995, 4009, and 3576 for those with no exposure; 284, 230, and 214 for those with 1 exposure; and 64, 50, and 44 for those with 2 or more exposures.

LD is defined; estimates of the proportion of children with ADHD who also meet LD criteria range from 10% to more than 90%.[20,27] Of the 5357 children analyzed in this birth cohort, 932 (17.4%) were diagnosed with LD (either reading, math, or written skills) before age 19, 341 (6.4%) were diagnosed with ADHD, and 240 (4.5%) were diagnosed with both. Common genetic influences may explain this overlap, at least in part.[28] Hypotheses to explain the relationship between ADHD and LD include that children with features of both have a qualitatively distinct condition (as supported by the genetic studies) and that there is a continuum of ADHD severity, with children with both ADHD and LD exhibiting more severe executive dysfunction compared with children exhibiting just ADHD.[20]

Several studies in rodents have shown that histologic neurodegeneration produced by neonatal exposure to anesthetics is associated with a diminished capacity to retain learned behaviors,[2,29] including a study that specifically examined the effect of repeated exposures in rodents and found a reduction in hippocampal neurogenesis (nonapoptotic) as well as profound deficits in learning and memory in later behavioral studies.[30] Fredrickson et al[9,29,31-34] found that ketamine given to neonatal rats produced hyperactivity that could be ameliorated by dextroamphetamine, which is used to treat ADHD. Studies using the rhesus monkey have produced histologic results that are similar to those observed in rodents.[3,4,35] Exposing neonatal monkeys to 24 hours of ketamine affects performance in tasks related to both learning and executive function (including motivation and working memory) up to 4 years after exposure (equivalent to human adolescence).[4] Thus, although these findings in rodents and nonhuman primates cannot be directly extrapolated to humans, it is plausible to postulate effects of anesthetic exposure on both learning and executive functions.

Children receiving anesthesia also experience surgery or other procedures, and it is possible that factors associated with the procedure itself could cause neurodegeneration. Accumulating evidence suggests that insults before and after birth, including stress[36] and inflammation,[37] may be associated with

TABLE 3. Exposure to Procedures Requiring Anesthesia Before Age 2 Years and Risk for ADHD

	Unadjusted		Covariate adjusted[a]		Propensity stratified[b]	
Variable	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Procedure/anesthesia exposure						
None (n=5007)	1.0[c]		1.0[c]		1.0[c]	
1 (n=286)	1.52 (1.02-2.25)	.039	1.35 (0.90-2.02)	.148	1.18 (0.79-1.77)	.414
≥2 (n=64)	2.59 (1.38-4.85)	.003	2.49 (1.32-4.71)	.005	1.95 (1.03-3.71)	.042
Total duration of anesthesia (min)						
Continuous (per 30 min)	1.03 (1.00-1.05)	.020	1.03 (1.01-1.06)	.015	1.02 (0.99-1.04)	.160
Categorical (min)						
0 (n=5007)	1.0[c]		1.0[c]		1.0[c]	
1-30 (n=65)	1.00 (0.37-2.68)	.999	1.00 (0.37-2.68)	.999	0.83 (0.31-2.24)	.715
31-60 (n=68)	1.64 (0.78-3.47)	.195	1.59 (0.75-3.36)	.229	1.34 (0.63-2.84)	.448
61-90 (n=90)	1.40 (0.69-2.83)	.347	1.06 (0.50-2.25)	.879	1.05 (0.52-2.14)	.884
91-120 (n=46)	2.50 (1.18-5.30)	.016	2.09 (0.98-4.43)	.055	1.83 (0.86-3.91)	.118
≥121 (n=81)	2.24 (1.23-4.08)	.009	2.23 (1.21-4.10)	.010	1.70 (0.92-3.15)	.089

[a] Analysis was performed using proportional hazards regression with covariates included for sex, birth weight, and gestational age. We excluded 336 individuals from the covariate-adjusted analysis because of missing covariate information. CI = confidence interval.
[b] Analysis was performed using stratified proportional hazards regression with 5 strata defined based on propensity score. We excluded 364 individuals from the propensity-stratified analysis because of missing data for variables included in the propensity score or because the propensity score was outside the range of overlapping scores for those exposed vs unexposed to anesthesia before age 2 years (see Methods).
[c] Reference value.

later adverse neurocognitive outcomes. For example, in an animal model of systemic inflammation produced by bacterial infection in early development, deficits in learning and memory are produced by increases in the cytokine interleukin-1β after later exposure to a "second hit" of lipopolysaccharide.[38] In another example, in infants with necrotizing enterocolitis, bacteremia is associated with developmental dysfunction, suggesting that systemic inflammation may affect the developing brain.[39] Surgery can produce stress and inflammatory responses in proportion to the severity of surgical injury.[40,41] However, it is unclear whether the magnitude of these responses produced by surgery or other procedures in our cohort (procedures that varied widely in intensity) are comparable to those produced in animal or human studies examining neurodevelopment. Also, anesthesia itself modulates these responses,[41] further complicating understanding of potential causative mechanisms.

When taken together with our prior analyses,[7,8] we find an association between exposure to multiple procedures requiring anesthesia and both LD and ADHD. Even though there is considerable overlap between these conditions,[27] similar results are found if those children with only ADHD are considered. The same is true if children with only LD are considered. In this cohort, there were 692 children (12.9% of the total cohort) who were diagnosed with only LD (no ADHD). If the propensity-stratified analysis is performed with this as the dependent variable, excluding children with ADHD, again multiple, but not single, exposures to procedures requiring anesthesia were associated with the diagnosis of LD before age 19 (HR, 1.11; 95% CI, 0.81-1.54; *P*=.51, and HR 2.26; 95% CI, 1.34-3.79; *P*=.002 for single and multiple exposures, respectively). To the extent that ADHD and LD are produced by distinct mechanisms, this suggests that exposure to procedures requiring general anesthesia may affect both.

In our prior analysis, we found no association between exposure to procedures requiring anesthesia and implementation of an IEP-EBD.[8] Typically, indications for an IEP-EBD include mood disorders such as anxiety and depression, unusual behavior patterns, and more severe forms of disruptive behaviors. Indeed, the majority of our children diagnosed with ADHD did not receive an IEP-EBD (eg, of the 341 children with ADHD in the entire cohort, only 79 [23%] had an IEP-EBD). It thus appears that any adverse effects of procedures requiring anesthesia on behavior were not of sufficient severity to trigger IEP-EBD implementation. Alternatively, because the requirement for an IEP-EBD captures a broad spectrum of behaviors of widely differing etiologies, one can postulate that the significant

TABLE 4. Exposure to Procedure Requiring Anesthesia Before Age 2 Years and Risk for ADHD After Excluding All Children With Learning Disabilities[a]

Variable	Unadjusted		Covariate adjusted[b]		Propensity stratified[c]	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Procedure/anesthetic exposure						
None (n=4156)	1.0[d]		1.0[d]		1.0[d]	
1 (n=226)	1.80 (0.91-3.58)	.093	1.56 (0.78-3.13)	.208	1.38 (0.68-2.78)	.374
≥2 (n=43)	4.32 (1.58-11.76)	.004	3.75 (1.31-10.71)	.014	3.32 (1.20-9.20)	.021
Total duration of anesthesia (min)						
Continuous (per 30 min)	1.03 (0.98-1.07)	.272	1.03 (0.98-1.08)	.299	1.02 (0.97-1.06)	.547
Categorical (min)						
0 (n=4156)	1.0[d]		1.0[d]		1.0[d]	
1-30 (n=56)	0.80 (0.11-5.76)	.827	0.80 (0.11-5.72)	.820	0.68 (0.10-4.91)	.703
31-60 (n=54)	2.44 (0.77-7.73)	.128	2.40 (0.76-7.61)	.138	1.95 (0.61-6.20)	.260
61-90 (n=66)[e]	0.0[e]		0.0[e]		0.0[e]	
91-120 (n=34)	7.26 (2.95-17.87)	<.001	5.61 (2.25-14.00)	<.001	4.93 (1.95-12.46)	<.001
≥121 (n=59)	3.12 (1.14-8.49)	.026	2.69 (0.94-7.64)	.064	2.38 (0.86-6.61)	.095

[a] This analysis excludes all patients diagnosed with learning disability (LD) before age 19 years (N=932; 240 had both LD and attention-deficit/hyperactivity disorder [ADHD] and 692 had only LD). CI = confidence interval.
[b] Analysis was performed using proportional hazards regression with covariates included for sex, birth weight, and gestational age.
[c] Analysis was performed using stratified proportional hazards regression with 5 strata defined based on propensity score.
[d] Reference value.
[e] No child in the 61-90 min anesthesia group had ADHD.

association between procedures requiring anesthesia and ADHD may reflect an effect on the risk for core aspects of ADHD (inattention, hyperactivity, and impulsivity) but not on associated severe behavior problems that trigger the need for IEP-EBD.

Limitations of analyses using this birth cohort have been extensively discussed.[14,15,42] To highlight the most salient limitation, as mentioned previously in this article, we cannot distinguish between the effects of anesthesia per se and the potential effects of the procedure or surgery accompanying the anesthesia. Also, children who require anesthesia may differ in ways relevant to the outcomes studied compared with those who do not. Although we attempted to control for health status using the ADG scoring system, this method may or may not capture relevant confounders and certainly does not adjust for family factors that may suggest genetic predisposition. Finally, there was substantial overlap between LD and ADHD in our cohort, and the relatively few children with only ADHD limits the statistical power to examine associations in these children. Nonetheless, we were still able to detect an association between multiple exposures and ADHD in these children with only ADHD.

CONCLUSION

In a population-based birth cohort, repeated exposure to procedures requiring general anesthesia before age 2 years was associated with increased risk for later development of ADHD. This result extends similar findings from this cohort for LD and group-administered tests of cognition and achievement, and points to defects in aspects of executive functioning as one potential phenotype of injury associated with procedures requiring anesthesia. In addition to providing insight into the possible consequences of undergoing procedures requiring anesthesia at an early age, these findings support the concept that environmental factors may be important in the pathogenesis of ADHD.

ACKNOWLEDGMENTS

We thank our colleagues Bob A. Rappaport, MD, Wendy R. Sanhai, PhD, and Chekesha S. Clingman, PhD, LCDR, USPHS, at the United States Food and Drug Administration for their support and their commitment to protecting the public's health. We acknowledge the late Leonard T. Kurland, MD, (Division of Epidemiology, Mayo Clinic, Rochester, MN) for his vision in initiating the Rochester Epidemiology Project. Finally, we would like to thank our research coordinator Shonie Buenvenida, RN, for help in abstracting the data and Mrs Theresa Hanson for secretarial help.

Drs Sprung and Flick and Mr Schroeder had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Drs Sprung and Flick contributed equally to this article.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org.

Grant Support: This study was funded by a United States Food and Drug Administration contract (HHSF223200810037C; Principal Investigator: Randall Flick, MD), Mayo Foundation for Medical Education and Research, Rochester, MN, the National Institutes of Health (Grant number R01 HS29745; Principal Investigator: William Barbaressi), and the Rochester Epidemiology Project (Grant number R01 AG034676; Principal Investigator: Walter A. Rocca, MD).

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