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A retrospective cohort study of the association of anesthesia and hernia repair surgery with behavioral and developmental disorders in young children

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Abstract

Recent animal studies have shown that commonly used anesthetic agents may have serious neurotoxic effects on the developing brain. The purpose of this study was to assess the association between surgery for hernia repair and the risk of behavioral and developmental disorders in young children. We performed a retrospective cohort analysis of children who were enrollees of the New

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Author Contribution Statement

All the authors made substantive contributions to the conceptualization and design of the study and all endorse the results and conclusions. Dr. DiMaggio, through a data use agreement with the US Centers for Medicare and Medicaid Services, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the analyses. He was also responsible for obtaining IRB approval, the initial drafting of the manuscript, as well as for critical revisions.

Dr. Sun suggested and guided analyses, and contributed to the interpretation of the data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content.

Dr. Kakavouli contributed to the interpretation of the data and analyses and critical revision of the manuscript for important intellectual content.

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Dr. Li contributed to the study design, statistical analysis, interpretation of the results, drafting of the manuscript, and critical revision of the manuscript for important intellectual content.

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Conflict of Interest Declaration

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York State Medicaid program. Our analysis involved following a birth cohort of 383 children who underwent inguinal hernia repair during the first three years of life, and a sample of 5050 children frequency-matched on age with no history of hernia-repair before age 3. After controlling for age, gender, and complicating birth-related conditions such as low birth weight, children who underwent hernia repair under three years of age were more than twice as likely as children in the comparison group to be subsequently diagnosed with a developmental or behavioral disorder (adjusted HR 2.3, 95% CI 1.3, 4.1). Our findings add to recent evidence of the potential association of surgery and its concurrent exposure to anesthetic agents with neurotoxicity and underscore the need for more rigorous clinical research on the long-term effects of surgery and anesthesia in children.

Keywords

Anesthesia; surgery; behavior; development

INTRODUCTION

Pre and peri-natal exposure to medical interventions, including drugs, has been implicated in a number of developmental, behavioral and psychiatric outcomes.[1] Recently, laboratory studies have suggested neurotoxic proapoptotic effects of anesthetic agents in infant rats and other animals.[2,3] Experimental data indicate that N-methyl-D-aspartatic acid glutamate receptor agonists (NMDA) and γ aminobutyric acid (GABA) receptor antagonists trigger cell death through translocation of Bax proteins on mitochondrial membranes causing leakage of cytochrome-c culminating in activation of caspase-3.[4]

This effect has been cited as a possible mechanism of fetal alcohol syndrome because alcohol is both an NMDA agonist and GABA antagonist.[4] Many anesthetic agents have one or both of these properties and the question has been raised whether these experimental animal data can be extrapolated to humans. Arguments against this hypothesis include high doses of an anesthetic agent such as ketamine being required to trigger apoptosis in infant rats, the vulnerable synaptogenic period in rats being short while extrapolation to humans would require frequent, repeated exposure over a long period of time, and that the effects in rodents might be due to hypoxia rather than the anesthetic agents, an effect prevented in the clinical setting through careful, continuous monitoring.[5]

The purpose of our study is to assess the association of hernia repair surgery under three years of age with subsequent behavioral and development disorders in a birth cohort of children enrolled in the New York State Medicaid program.

MATERIALS AND METHODS

The study protocol was reviewed and approved by the Institutional Review Board of Columbia University.

Data Sources

We conducted a retrospective analysis of New York State Medicaid Analytic Extract (MAX) files for 1999 to 2002.[a] These are a complete set of person-level data files on all New York State residents eligible for health care services under the state Medicaid program.

[a]CMS. Medicaid Analytic eXtract (MAX) General Information Centers for Medicare and Medicaid Services (Washington), 2006. (http://www.cms.hhs.gov/MedicaidDataSourcesGenInfo/07_MAXGeneralInformation.asp).

The data files are compiled by the Centers for Medicare and Medicaid Services (CMS) from claim information provided by the New York State Department of Health. Health care providers submit standardized claims[6] that include clinical information that is most commonly abstracted from patient charts by non-clinician administrative personnel. Race and ethnicity designations are based on administrative data collected by CMS from information provided by enrollees as part of their application. CMS routinely conducts validation studies of MAX data[b] and researchers have analyzed and validated the reliability of these data for studies of outpatient psychiatric and behavioral diagnoses in New York State.[7]

Cohort

We identified all children who were born in the state of New York between 1999 and 2001 and who were covered under the Medicaid system by searching the MAX files for system-specific codes for maternal and newborn admissions as well as delivery-related first or primary ICD-9[8] "V series" diagnosis codes. For each uniquely identified birth, we searched primary and secondary ICD-9 codes for any of 41 delivery or birth-related diagnosis that might indicate a complication.[††]

We used a unique Medicaid patient identifier to match birth records to service utilization indicator records for the years 1999–2002, searching for and removing duplicate records at each stage of the merge. Because they may not have had complete ICD-9 diagnoses for each visit, we removed records for children who were enrolled in a managed care or capitated insurance program at any time during the 4-year period.

We defined "exposure" as the presence of an inpatient or outpatient principal or secondary ICD-9 procedure code related to hernia repair (4642, 530–539, and 9627). We defined a behavioral or developmental "outcome" as the presence of a diagnostic code for unspecified delay or behavioral disorder (3159 and 3129), mental retardation (317–3195), autism (299) and language or speech problems (3153). We excluded records for which the date of an outcome diagnosis preceded that of hernia repair.

Our analysis included all children who underwent hernia repair during the study period 1999–2002 and a random sample of children who did not have hernia repair during that time. The unexposed group may have had anesthesia exposure for other reasons. The two groups of children were frequency-matched on age in months.

STATISTICS

We tabulated information on patient age in months, gender, race, secondary birth-related diagnoses that might be confounders, date of exposure and date of outcome diagnoses, and loss to follow up. We compared variables between the two groups of children using t-tests for continuous variables and X^2 tests for categorical variables setting statistical significance at 0.05.

Person time of observation was calculated as the time in days from entry into the cohort through birth, until either the date of the first outcome diagnosis, death, last day of the year in which a child was lost to follow up, or the end of the study period.

[b]Medicaid Analytic eXtract (MAX) General Information, Centers for Medicare and Medicaid Services (Bethesda), 2006. (http://www.cms.hhs.gov/MedicaidDataSourcesGenInfo/07_MAXGeneralInformation.asp).

[††]A list of the ICD-9, V-series diagnostic codes used to identify births to establish retrospective birth cohort, and the ICD-9 diagnostic codes used to identify deliveries with complications is available from the authors.

We calculated unadjusted incidence density ratios comparing the two groups of children for the number of developmental/behavioral diagnoses using the number of years of observation for the study period for each group. We then analyzed the data using Cox proportional hazards models controlling for age, gender, race and presence or absence of any complicating birth-related diagnoses, with survival defined as the time in days of person-time of observation as defined above. We performed the statistical analysis using Statistical Analysis Software version 9.1 (SAS Institute, Cary, NC).

RESULTS

There were 112, 851 non-managed care, fee for service birth records for the period 1999 to 2001. Of these children, 93,317 (82.7%) remained in the cohort for the entire 4-year period. One thousand seven hundred fifty two children (1.5%) were lost before the second year of follow up, 12,471 (11.1%) were lost during the second to third year of follow up, and 5,311 (4.7%) were lost during the 4^{th} year of follow up.

Children who were lost to follow up were slightly less likely to be female (48.0%) than children who were not lost to follow up (48.9% female) (p=0.0001) and had on average a hospital stay of 4.6 days during birth as compared to 4.0 days for those who were not lost to follow up (p=0.0001).

Among the birth cohort, 383 had diagnostic codes for hernia repair during the study period. This group was frequency-matched on age to 5050 children from the same birth cohort who did not have hernia repair. There was no statistically significant difference between exposed and unexposed children on loss to follow up (18% vs. 17.8%, p=0.6)

At the end of the follow-up (December 30^{th}, 2002), the mean age of the study cohort was 30 months, ranging from 12 months to 48 months. There was no statistically significant difference in age between the hernia repair group and the comparison group. Children who underwent hernia repair were more likely to be male (78% vs. 50%), were more likely to be Black and less likely to be white or Hispanic than children in the comparison group (Table 1).

Children who had hernia repair were more likely than children in the comparison group to have had at least one of the pre-defined potentially confounding complicating diagnoses at birth (77.0% vs. 32.9%, p<0.0001) (Table 2). The most common confounding diagnosis at birth among children in the hernia repair group was low birth weight (31.6%), followed by peri-natal hypoxia (16.5%) and peri-natal infection or hemorrhage (14.4%). The most common confounding diagnosis at birth among the children in the comparison group was peri-natal infection or hemorrhage (13.4%) followed by low birth weight (11.7%) and congenital CNS anomaly (3.8%).

Of the children who had hernia repair, 17 (4.4%) were diagnosed with a behavioral or developmental disorder compared to 59 (1.2%) in the comparison group. The incidence rate of behavioral and developmental disorders was 19.6 cases per 1000 person-years for the exposed group and 5.4 cases per 1000 person-years for the unexposed group (unadjusted rate ratio 3.6, 95% CI 2.1, 6.2)

In a Cox Proportional Hazard model controlling for age in months, gender, race and the presence of a confounding diagnosis at birth, children who underwent hernia repair were more than twice as likely to have had a behavioral/developmental outcome than children in the comparison group (HR 2.3, 95% CI 1.3, 4.1; Table 3). There was a similarly increased risk associated with male gender. A survival curve comparing the cumulative probability of not having a behavioral/developmental diagnosis between the two groups of children is presented in figure 1.

DISCUSSION

Our results indicate a statistically significant association between hernia repair under three years of age and an increased risk of behavioral/developmental disorders. Though subject to a number of important limitations, the epidemiological evidence persisted despite identifying and correcting for potential confounding variables, including low birth weight. The results of our cohort analyses are consistent with prior human prenatal and perinatal studies[9,10] and help establish a possible association between the exposure early in life to surgery/anesthesia and an increased risk of subsequent developmental delays and behavioral problems.

Our findings are in line with increasing interest in life-course epidemiology[11,12] which has demonstrated a number of behavioral and psychiatric sequelae late in life attributed to pre and peri-natal health care interventions.[13–17] The results of such investigations present us with, as Bresnahan and Susser[1] aptly put it, “the paradox that interventions known to be beneficial for infants and children may have unintended adverse consequences in adulthood.”

Anesthetic agents have been implicated in such adverse consequences. In a case series comparing 11,939 births in a hospital that routinely administered valium and ketamine during delivery to 19,580 births in 3 hospitals where non-anesthetic deliveries were common, there were 21 cases (0.2%) of autistic disorder in the anesthetic-exposed group compared to 18 cases (0.09%) of autistic disorder in the unexposed group for a statistically significant difference.[9] In a matched case-control study of 694 mothers of children with central nervous system defects, 12 (1.7%) reported first trimester general anesthesia exposure, compared to 34 (1.1%) of 2,984 matched controls, yielding an odds ratio of 1.7 (95% CI 0.8, 3.3).[10]

Our study has several limitations. First, the administrative data set used in this study is a blunt instrument to establish precise exposures and clinical outcomes. Such an approach is invariably subject to measurement error. While we believe the assumption underlying our exposure variable, that an ICD-9 procedure code indicating herniorrhaphy indicates exposure to anesthesia, is reasonable, we could not, due to the limitations of the data set, explicitly establish type, route, or dose of anesthetic administered. Perhaps more importantly, we cannot, based on this data, differentiate the effects of anesthesia from those of the surgery. Moreover, ICD-9 diagnoses for behavioral and developmental disorders for young children might be susceptible to bias resulting from misclassification, underreporting and local practice patterns.

Second, our findings are subject to bias from unmeasured confounders. Even within the relatively homogeneous Medicaid population, the groups we compared differed in many important ways, including gender, race, and complicating diagnoses. Although we were able to adjust for some important variables, such as low birth weight, we could not take other potential confounding factors, such as an explicit indicator for prematurity, into account due to the lack of data. In this instance, since premature infants would have low birth weight, it is likely the confounding contribution of prematurity has been substantially addressed. Out data, though, did not address other potentially important covariates such as prolonged mechanical ventilation in ex-premature infants who develop inguinal hernia. Children who undergo hernia repair early in life differ in important ways from those that do not, and this may have implications for the design of future prospective studies.

Third, Medicaid is a jointly funded health insurance program provided by federal, state and local governments, with locally determined income, age, and disability requirements. The reliability of using Medicaid databases for analyzing behavioral and developmental diagnoses[7] has been validated, but this vulnerable group differs from the general population in ways that affect their health and medical care utilization,[18] and that make them more likely to suffer mental illness.[19] And, while Medicaid provides coverage to 26% of all children in the

U.S (50% of all low-income children), 37% of all pregnant women, these results cannot necessarily be generalized to other population groups.

In other respects, some of the imprecision or 'noise' in the data, such as misclassifications in our comparison groups, would lead to an underestimate of the true association between anesthesia and hernia repair with outcome. The more children in the no-hernia group who were, in fact, exposed to anesthesia and surgery, the more the hazard ratio would underestimate the true risk. Similarly, the greater the use of regional/local anesthesia in the hernia repair group, the more the observed hazard ratio underestimates the true effect of general anesthesia.

Our study has the advantage of looking at more recent clinical practice than perhaps one based on exposure occurring many years ago. The disadvantage is that we had access to only 2 to 3 years of post-surgery data. We cannot, based on these data, determine the longer term effects of the exposure and the natural history of the developmental and behavioral outcomes. We plan to address these important questions by continuing and expanding our effort to follow up the study subjects.

Our study indicates that children undergoing hernia repair under three years of age are at an increased risk of being subsequently diagnosed with behavioral/developmental disorders. The association between hernia repair surgery and subsequent behavioral/developmental disorders could not be explained by such confounding factors as low birth weight, co-morbidity, and demographic characteristics. Given the implications for clinical practice and health policy of our findings, there is an urgent need for more rigorous epidemiologic studies to assess the long-term health effects of exposure to surgery and anesthesia in children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

NMDA	N-methyl-D-aspartatic acid glutamate receptor agonists
GABA	γ – aminobutyric acid
CMS	Centers for Medicare and Medicaid Services
ICD	International Classification of Diseases
MAX	Medicaid Analytic Extract

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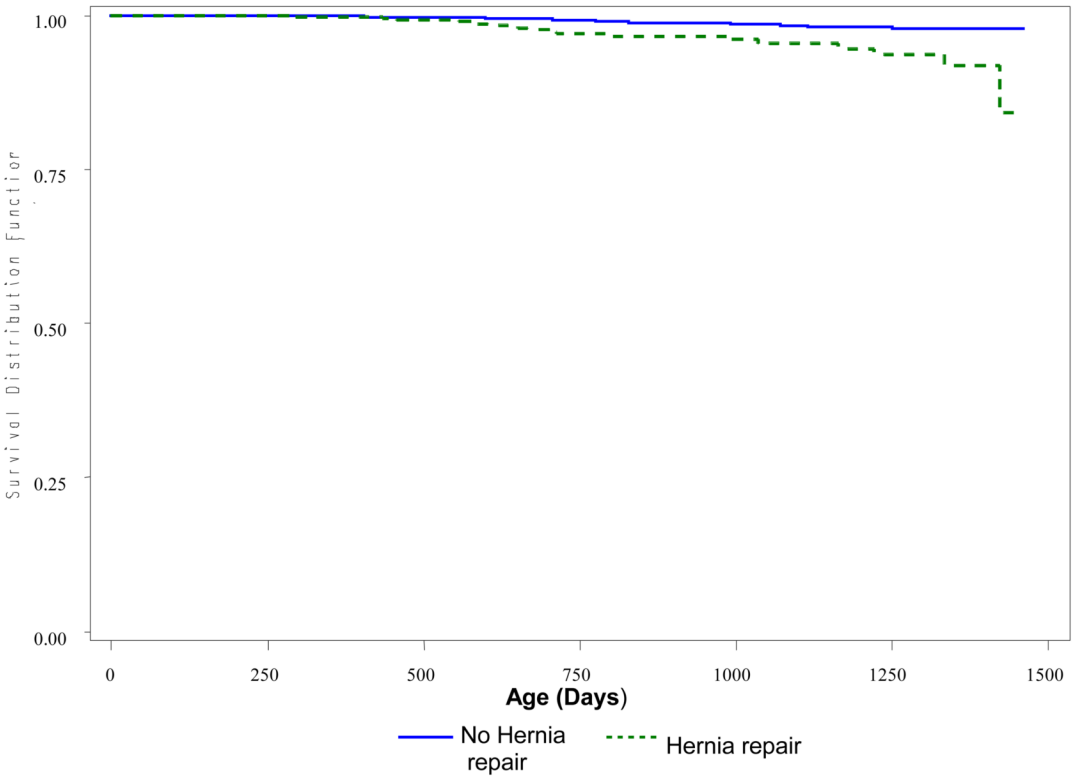

Figure 1.
Cumulative probability of not having a diagnosis of behavioral and developmental disorders for children undergoing herniorrhaphy under three years of age and children in the comparison group. Retrospective birth cohort, New York State Medicaid data, 1999–2002.

Table 1

Race/ethnicity by exposure status, Herniorrhaphy vs. random sample, retrospective birth cohort, New York State Medicaid data, 1999–2002.

Table of exposure by race							
	Race/Ethnicity						
	White	Black	NativeAmerican	Asian	Hispanic	Unknown	Total
No Hernia Repair	1929	1010	116	216	1006	773	5050
	(38.2)	(20)	(2.3)	(4.3)	(19.9)	(15.3)	
Hernia Repair	117	112	4	13	48	89	383
	(30.6)	(29.2)	(1)	(3.4)	(12.5)	(23.2)	
Total	2046	1122	120	229	1054	862	5433

Table 2

Secondary birth-related diagnoses, herniorrhaphy vs. random sample, retrospective birth cohort, New York State Medicaid data, 1999–2002. (Statistically significant differences indicated by asterix)

Table of exposure by second diagnosis at birth			
	No Hernia Repair	Hernia Repair	Total
*No second diagnosis	3389(67.1)	88(23.0)	3477
Parasitic Infection	17(0.3)	5(1.3)	22
Neoplasm	8(0.2)	0(0)	8
Endocrine, Metabolic, Immune Hematologic	6(0.1)	2(0.5)	8
Alcohol and Drug	2(0.04)	0(0)	2
Ear, Nose and Throat	3(0.1)	1(0.3)	4
Cardiac and including Rheumatic	7(0.1)	0(0)	7
Respiratory including pneumonia	2(0.04)	0(0)	2
*Gastrointestinal including hernia	4(0.1)	6(1.6)	10
Genitourinary including Renal	13(0.3)	1(0.3)	14
Complications of pregnancy and labor	2(0.04)	0(0)	2
Dermatologic and musculoskeletal	20(0.4)	0(0)	20
*Congenital Anomaly CNS	193(3.8)	40(10.4)	233
*Low Birth Weight (<2500 grams)	592(11.7)	121(31.6)	713
*Perinatal hypoxia	75(1.5)	63(16.5)	138
Perinatal infection hemorrhage hemeotological	678(13.4)	55(14.4)	733
Ill-defined signs symptoms	18(0.4)	0(0)	18
Infectious Disease Exposure	21(0.4)	1(0.3)	22
TOTAL	5050	383	5433

Table 3

Cox proportional hazard ratios and 95% confidence intervals (CI) for behavioral and developmental disorders associated with hernia repair controlling for age, gender, race and complicating diagnosis at birth, New York State Medicaid data 1999–2002.

	HAZARD RATIO	95% CI
Anesthesia Exposure	2.3	1.3, 4.1
Age (months)	1.0	0.9, 1.0
Sex (male vs. female)	2.7	1.5, 4.7
Race (other vs. white)	1.1	1.0, 1.1
Birth Complication[##]	1.6	1.1, 2.5

[##] Defined as the presence or absence of any of the 17 secondary birth-related diagnoses listed in table 2.