Cognitive development in children and age at the time of first anesthetic exposure: a pilot study

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Introduction

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[1-4], but human data are lacking. We performed a retrospective pilot study to test the feasibility and calculate power 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.

Patients and Methods

Neurocognitive development was assessed using a validated 120-item parental questionnaire (CBCL/4-18[5]) in 250 children who were operated for pediatric urological procedures between the ages of 0 and 6 years (1987-1995). Pediatric urological procedures may be performed at any age, but the timing of surgery depends mainly on the age at which a diagnosis is made. 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 opioid was rarely used. For selected procedures general anesthesia was sometimes supplemented with a caudal epidural block.

Results

Of 249 questionnaires returned, CBCL/4-18 was clinically deviant in 41 (23%) of children aged <24 months at the time of first surgery and 13 (20%) aged > 24 months (table 1). Table 2 shows potential confounders and table 3 shows the crude and adjusted odds for a clinically deviant CBCL 4/18 score. A trend towards increased risk with younger age was present, but the confidence intervals were very wide.

Table1: 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	> 24 months
	(n = 243)	(n = 178)	(n = 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 CBCL/4-18 problem score according to Dutch norms15 are: boys 4-11 yrs: 40; girls 4-11 yrs: 36; all 12-18 years: 37.

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	> 24 months
	(n = 243)	(n= 178)	(n = 65)
Patient characteristics			
Boys, n (%)	183 (75.3)	144(80.9	39 (60.0
Age at anesthesia (mo)	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 (mo)	40 (38 - 41)	39 (37 - 40)	40 (39 - 41)
Birth weight (g)	3300 (2865-3855)	3300 (2845-3845)	3310 (3000-3850)
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: Influence of age at the time of first anesthesic exposure on the presence of a clinically deviant CBCL/4-18 score

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		Odds ratio (95% CI) for age at time of first anesthesia (months)			
Model nr.	description	<6 months (n = 84)	6 – 12 months (n = 44)	12- 24 months (n = 50)	> 24 months (n = 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

CI: confidence interval; CBCL: Child Behaviour Checklist. Odds ratios are based on logistic regression modeling.

Patients who underwent their first anesthetic after 24 months of age serve as the reference group.

Conclusions

We 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 2268 to 6020, dependent on the age groups that are being compared. Given these numbers, a large scale collaboration is required for a future study. The unbreakable association between surgery and anesthesia will be a limitation in all study designs, both retrospective and prospective

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