Early Childhood Anesthetic Neurotoxicity and Unmeasured Covariates: There's the RUB

To the Editor:

In retrospective investigations that use cognitive and intellectual test data as endpoints, the potential for a wide variety of medical and sociologic covariates to influence the results is well recognized. Investigations of the effect of anesthetic exposure during infancy have invariably attempted to take these potential covariates (including birth weight, prematurity, parental presence and education, gender, the disease process that led to the anesthetic, and coincident disease processes) into account. The thoroughness of that process is critical to any interpretation or extrapolation of the conclusions.

In that light, I write to request additional information about the 112-child subset of the Raine cohort who were the subject of the recent report by Ing *et al.*[1] Their investigation suggested that even very brief anesthetic exposure in the first 3 yr of life results in adverse effects on the development of language skills.

First, I request that the authors provide a table of the surgical procedures, analogous to that provided in their original article about the Raine cohort.[2] Many of the children in that first cohort underwent upper airway procedures (mygingotomy and tubes, tonsillectomy and adenoidectomy, cleft lip and palate repair, tracheostomy) that might well have some relevance to the acquisition of language skills. At a minimum, chronic middle ear effusions are known to be associated with "impairments of receptive language and verbal aspects of cognition."[3] Furthermore, prospective study of children with middle ear effusions has failed to demonstrate subsequent differences in language skills between those who do and do not undergo mygingotomy and tubes, suggesting that the adverse effect of middle ear effusions cannot be assumed to have been rectified by their mygingotomy and tubes procedures.[4] What do the authors and the editorialists[5] think of the potential for a contribution by those disease states to the deficits that were identified?

Second, were any subjects excluded on the basis that the disease states necessitating the procedures or the treatment thereof might have an impact on learning and development? In the very careful retrospective study by Block *et al.*,[6] the apparently appropriate exclusions entailed fully 56% of anesthetized children who were otherwise eligible on the basis of complete records. In addition to the airway-related procedures mentioned above, the original Raine included procedures requiring cardiopulmonary bypass, operations involving the orbit or retina, cranioplasty, tracheostomy, dialysis access. I am concerned that many of these might reasonably be expected to influence cognitive development, either directly or indirectly. Not incidentally, these issues may have influenced other studies that have reported an association between anesthetic exposure and cognitive development. Twenty-six percent of the children in the two Olmsted county cohort studies underwent unspecified "Ear, nose, and throat" procedures and 11.5% underwent neurosurgical or ophthalmologic procedures.[7,8]

In connection with the same concern about the influence of coincident disease processes, Ing *et al.* calculated a Resource Utilization Band (RUB) score to estimate, based on the number of International Classification of Diseases, Ninth Revision, diagnostic codes, the potential impact of comorbidities on neuropsychological test scores. Figure 2 of their study provides data for the original Raine cohort of 2,868 children, comparing RUB-corrected and RUB-uncorrected neuropsychological and academic achievement scores.[1] For every metric, that correction moved the CI bar closer to the line of no effect, reminding us of the potential for the intrusion of comorbidities. However, those same RUB correction data, as described in the Methods section, are not provided for the restricted cohort described in the present article (their fig. 1).[1] What did the RUB correction reveal? Incidentally, those many of us who are unfamiliar with RUB scores will wonder why the RUB-driven percentage change in the various scores (fig. 2) is not the same for every cognitive metric. The editorialists did not comment on this correction process.[5] I would like to know whether they have scrutinized this correction method and whether they accept its validity, both qualitatively and quantitatively.

Finally, a correction for gender was applied. This is necessary and appropriate because there was a male preponderance in the exposed subset of children and males are known to perform less well on standardized testing in general and on language-oriented tests in particular.[3,9,10] The methodology was not specified. Again, were the reviewers and the editorialists privy to information about that correction and can we the readers of Anesthesiology be confident that it is qualitatively and quantitatively valid? To give us further insight into the impact of the gender variable, can the authors perform a statistically meaningful comparison of exposed boys (n = 73) *versus* unexposed boys (n = 333).

This is an all but terrifying issue for parents. Accordingly, I think that investigations of this topic should be tempered by the most rigorous consideration of the possibility that apparent neurotoxic effects of anesthetics might represent the intrusion of medical and sociologic covariates. I hope that the authors[1] and the editorialists[5] will provide the readership with information and informed opinion as to the potential impact of comorbidity-related influences on the association between anesthesia during the first 3 yr of life and impairment of language skills.

Competing Interests

The author declares no competing interests.

This letter was sent to the author of the referenced Editorial View, who declined to reply.

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In Reply:

We thank Dr. Drummond for his interest in our work.[1] In response to his request, we have provided a table of surgical procedures performed in the restricted cohort of children who had data on all outcomes and covariates of interest (table 1). We also have applied the resource utilization band (RUB) comorbidity correction to our restricted cohort as requested and found that the risks of deficit in the restricted cohort were consistent with those reported in the full cohort. However, because of the smaller sample size of the restricted cohort, two of the outcomes could not be modeled after adding RUB, and the remaining outcomes had wider 95% CIs than those reported in the full cohort. We would emphasize again that the primary purpose of the restricted cohort analysis was not to quantify the relative risk of cognitive deficits associated with the exposure to anesthesia, but rather to assess whether certain outcome measures were more sensitive than others in measuring differences between the exposed and unexposed children.

Table 1. Procedures Performed on Children Exposed to Anesthesia in the Restricted Cohort (n = 781)

Procedure	n (%)
Myringotomy	38 (24.5)
Inguinal and umbilical hernia	16 (10.3)
Dental Procedure	14 (9.0)
Minor skin and nail procedure	10 (6.5)
Orchiopexy, hydrocele, and varicocele	10 (6.5)
Tonsillectomy and adenoidectomy	10 (6.5)
Circumcision	8 (5.2)
Procedure on extraocular muscles	7 (4.5)
Hypo/epispadias repair and chordee release	6 (3.9)
Finger and hand surgery	5 (3.2)
Procedures on month/tongue and cleft lip and palate repair	5 (3.2)
Nasolacrimal duct probe	4 (2.6)
Computed tomography scan	3 (1.9)
Foot and knee surgery	3 (1.9)
Lymph node excision	2 (1.3)
Minor rectal/anal procedure	2 (1.3)
Nasal airway procedure	2 (1.3)
Procedure on orbit, lens, or retina	2 (1.3)
Tracheostomy and removal	2 (1.3)
Bone marrow biopsy	1 (0.6)
Crainiectomy	1 (0.6)
Gastric and bowel repair and resection	1 (0.6)
Laparotomy and laparoscopy	1 (0.6)
Magnetic resonance imaging	1 (0.6)
PDA ligation	1 (0.6)
Total	155 (100)

Due to patients with multiple exposures, the number of procedures exceeds the number of exposed patients.

PDA = patent ductus arteriosus.

Comorbid illnesses including otitis media are potential confounders and may play a role in the cognitive outcome differences between children exposed and unexposed to anesthesia. Although 33% of the procedures in the full Raine cohort were otolaryngological in nature, they were unlikely to sufficiently explain the observed excess risk of cognitive deficits in the exposed children because similar results have been reported in children who underwent inguinal hernia surgery only.[2] In addition, the association between otitis media and developmental outcomes is disputed, with a meta-analysis of prospective studies finding the association to be negligible.[3]