Anesthesia in Childhood and Neurodevelopmental Outcome

The Ongoing Hunt for a Phenome

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THE question of whether or not anesthesia exposure in early childhood causes long term neurodevelopmental harm continues to attract attention. There is already good evidence in humans that surgery and anesthesia in early childhood is not associated with a global neurodevelopmental deficit. However, investigators continue to seek to determine whether specific deficits occur in particular neurodevelopmental domains to identify the so called "phenome" of injury. In this issue, Walkden *et al.* present data extracted from a large birth cohort and explored the relationship between exposure to anesthesia and surgery before 4 yr of age and a range of neurodevelopmental outcomes tested at ages 7 to 16 yr.[1] The Avon Longitudinal Study of Parents and Children (ALSPAC) recruited more than 14,000 pregnant women in 1991 and 1992 and have intensively followed their children. The birth cohort is one of the most complete in the world and has produced a wealth of data about other environmental and genetic determinates of health and development. Birth cohorts often contain complete longitudinal outcome data in multiple neurodevelopmental domains, making them an obvious resource to assist in defining any association between surgery and anesthesia in early childhood and later development. Indeed, previous researchers have similarly looked for such associations in the Western Australian Pregnancy Cohort (Raine) study.[2] The Raine Cohort study included 2,900 pregnant women between 1989 and 1992, and like the ALSPAC cohort, the children were followed up with detailed neurodevelopmental testing into their teens.

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The anesthesia exposure substudy of the Raine Cohort examined neurodevelopmental scores across areas of language, cognitive function, motor skills, and behavior in children tested at 10 yr of age with 11 different scores.[2] Scores were compared between children that were exposed to surgery and anesthesia before 3 yr of age and those that were not exposed. Evidence for an association between poorer performance and exposure was found in three of four scores in language and one of three in cognition.[2] They found no evidence for an association in the other seven scores, including no evidence for an association in the three behavioral scores and the motor score.[2]

The ALSPAC anesthesia exposure substudy was larger and had more detailed testing compared to the Raine anesthesia exposure substudy. The ALSPAC anesthesia exposure substudy reports the results for neurodevelopmental outcomes in 46 different scores across areas of motor, cognitive, linguistic, educational, social, and behavioral outcomes.[1] The study did not find that general anesthesia and surgery were associated with deficits in general cognitive ability, attention, sociocognitive function, working memory, reading and spelling performance, phonological awareness, verbal comprehension or expression, behavioral difficulties, or national assessments of English, mathematics, and science ability. There was, however, evidence for an association between exposure to surgery and anesthesia and dynamic balance scores, manual dexterity performance, and social communication scores.

Image: C. Brodoway, A.I. duPont Hospital for Children.

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In terms of statistically significant associations, the ALSPAC and Raine anesthesia exposure substudies have produced discordant results. This lack of concordance between outcomes is a feature of many of the larger studies examining neurodevelopmental outcome after surgery and anesthesia.[3] The Pediatric Anesthesia and Neuro Development Assessment (PANDA) cohort study,[4] the Mayo Anesthesia Safety in Kids (MASK) cohort study,[5] and the General Anesthesia Spinal (GAS) trial[6] are three of the larger studies with in-depth prospective neurodevelopmental testing, and again, no statistically significant associations were found in the same neurodevelopmental domain across all three studies.

How should we interpret the steadily increasing number of human studies where there is evidence of an association in one outcome domain in one study but not in another?[3] One explanation could be that the "positive findings" in each study are spurious and simply due to type one error. These studies often have multiple outcomes so the risk of type one error increases. This, however, is partly mitigated by the corrections for multiple testing made in both the ALSPAC and Raine anesthesia exposure substudy analyses. Another explanation for the disparity between studies may lie in the way we construct hypothesis testing. To test a hypothesis, we need to choose an arbitrary *P* value to drive the dichotomous decision to reject the null hypothesis or not—statistically significant evidence or not. The choice of 0.05 for such a *P* value is arbitrary and the adjustments to the threshold of 0.05 to account for multiplicity are inherently arbitrary too. This dichotomy drives us to conclude whether particular studies found evidence for an association—or not—in each domain tested. As samples of similar populations inevitably vary in their characteristics, it is expected that results in similar populations may produce different conclusions when conclusions are based simply on dichotomous thresholds. This problem is partly overcome by having large samples to increase the precision or confidence in the estimate of the effect in each study. Unfortunately, having to adjust for multiple outcomes significantly compromises that precision; so that even large studies have a limited capacity to produce definitive results. Replication can help. As more and more studies are done, there is more capacity to compare outcomes across studies, which increases the overall precision of the estimate of evidence for an association in each of the neurodevelopmental domains. That is why all these somewhat similar neurodevelopmental outcome studies are valuable and why, if they are performed carefully, they should be published. From a purely statistical point of view, no single study should be regarded as definitive in any domain, but rather, they all contribute to the cumulative evidence. This is of course why carefully performed systematic reviews and meta-analyses may, depending on the overall quality of the studies, provide stronger levels of evidence compared to individual studies.

Pertinently, the most recently published systematic review in this area (which was published before the ALSPAC anesthesia exposure substudy) acknowledged that while many individual studies have found associations in various neurodevelopmental domains, when all studies were considered, there was no evidence to conclude there is any association in any particular domain.[7] Systematic reviews in this area are, however, inherently and significantly limited due to the heterogeneity between studies.[8] The studies use different neurodevelopmental tests and assess children at different ages.[8] Apart from the difference in outcome measures, another explanation for the disparity in results between different studies could be that surgery and/or anesthesia may indeed cause some injury, but the impact of the injury varies depending on the timing of exposure and the population exposed. This is biologically plausible. The response to any brain insult during brain development depends on the timing, nature, and location of the injury, as well genetic and environmental factors. Thus, it is perhaps not surprising that no "phenome" for the impact of anesthesia and surgery has emerged.

What if a replicable "phenome" were to emerge among the cohort studies? Would this alone provide enough evidence to change practice? No, it would not. Confounding remains the most significant limitation to all observational studies, including the ALSPAC anesthesia exposure substudy. There are numerous known, and possibly many unknown, confounding factors when it comes to the association between exposure to anesthesia and neurodevelopmental outcome. This includes the likelihood of baseline comorbidities, indications for the procedure, and all the other perioperative factors which might influence neurodevelopment. Increasing sample size does not remove the risk of confounding as the confounding grows with the size of the study. Statistical adjustments and careful matching can reduce the impact of confounding but cannot eliminate it. Importantly, confounding can also explain any concordance of associations between studies. The same confounders may have the same impact on similar studies. If a "phenome" emerged, there is no surety it adds much to the likelihood that surgery and/or anesthesia actually causes significant brain injury. Randomized trials are the optimal way to reduce confounding but, when it comes to addressing this particular problem, they are logistically very difficult to design and conduct. To date, the General Anesthesia Spinal trial is the only trial designed specifically to assess the impact of anesthesia exposure in infancy and on long-term neurodevelopmental outcomes.[6]

Lastly, it is often assumed that any association between anesthesia and surgery and neurodevelopmental outcome must be linked to the preclinical neurotoxicity data observed in laboratory animals. This is a potentially flawed concept given the translational paradox of developmental anesthesia neurotoxicity research, where initial laboratory observations—and not a clinical phenome—seem to drive

clinical investigations.[9] This link is further weakened by the problem that the complexity of neurodevelopment makes it very difficult to translate laboratory findings to human neurodevelopmental outcomes. Laboratory studies are not particularly helpful in "guiding" us to where we might find a phenome. Even if a "phenome of injury" emerges in human studies where anesthesia and surgery is associated with poor neurodevelopmental outcomes, we still cannot assume it is linked to laboratory neurotoxicity data as there are many areas of perioperative care that may plausibly influence neurodevelopmental outcomes, such as cerebral perfusion, physiologic stress, inflammation, nutritional and metabolic changes, pain, and psychologic factors. Most of these have not been widely investigated in laboratory or preclinical settings. For example, little is known in infants about the interaction of hypotension, surgery, and anesthetics on brain homeostasis.

In conclusion, given the complexity of human neurodevelopment, no single study is ever likely to fully define the existence, or not, of an association between anesthesia and surgery in childhood and a particular deficit in later neurodevelopment. This possible problem can only be confirmed or refuted with the synthesis of evidence of multiple large and high-quality cohort studies, and preferably randomized trials, supported by sound and relevant preclinical data. The synthesis of the evidence is inherently a difficult task and so far, there is no coherent "phenome" for an association between surgery and anesthesia in children and adverse neurodevelopmental effects. The hunters remain empty handed.

Competing Interests

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