Repeat anaesthesia: what are the effects?

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“Early exposure to anesthesia and learning disabilities in a population-based birth cohort” was published in Anaesthesiology in March 2009. Wilder et al studied the association between anaesthesia before the age of four and the development of learning disabilities (LD), and found that, while a single anaesthetic was not associated with an increased risk of LD, receiving two or more anaesthetics was associated with an increased risk of LD (hazard ratio 1.59 for two anaesthetics, and 2.60 for ≥ three exposures). The risk for LD increased with longer cumulative duration of anaesthetic exposure.

Their findings were published in Time magazine under the headline “Anesthesia in infancy linked to later learning disabilities”, sparking much debate and fear in the lay press about anaesthesia in childhood, and drawing criticism and accusations of sensationalism from the world of academic anaesthesia.

The research behind this controversy goes back to the 1980s, and hinges on a basic understanding of embryology.

The developing brain and apoptosis

Neural development extends from the embryonic period through to adolescence. Various parts of the brain develop at different times and have different windows of vulnerability.

Developing neurons need to:
• Proliferate;
• Migrate;
• Differentiate; and
• Communicate.

Communication requires the development of synapses (synaptogenesis), which consists of biochemical and morphological changes both pre- and postsynaptically. In humans, the period of synaptogenesis extends from the third trimester up until 24 months after birth. In rats, it is mostly a postnatal phenomenon, occurring in the three weeks after birth.

Apoptosis - or programmed cell death - is essential for the normal development of the nervous system. It occurs during synaptogenesis commonly to remove neurons that are considered redundant. Apoptosis is an energy-dependent process mediated by cellular enzymes, including the group of proteases known as caspases. The targeted neuron dies with its membrane intact, and is rapidly phagocytised without stimulating an inflammatory response. This is in contrast to pathological neuronal necrosis, where cellular contents leak into the interstitium and trigger an inflammatory response. Up to 50-70% of neurons will be removed by physiological apoptosis during normal development.

Apoptosis can be triggered by various stimuli, including cytokines, hormones, viruses and toxic neurological insults.

Of mice and men

In neonatal rats (and mice, guinea pigs, and non-human primates) apoptosis can be triggered by blocking NMDA-receptors, or by activating GABA-receptors during the critical period of synaptogenesis. In this period, the NMDA-receptor is extremely sensitive to excitotoxic degeneration, so if the receptor is even transiently blocked, apoptotic neurodegeneration can be triggered.

Apoptosis in several animal species has been demonstrated after exposure to:
- Ketamine;
- Propofol;
- Isoflurane;
- Midazolam;
- Nitrous oxide (N₂O); and
- Barbiturates.

The effects seem to be dependent on both dose and duration of anaesthetic exposure. Combinations of drugs (especially combinations which act at both NMDA- and GABA-receptors) induce worse injury than single drugs.

The concern is that apoptosis, with its associated inhibited synaptic formation and neurogenesis, leads to later neurocognitive dysfunction, especially in the areas of learning and memory, and to neuro-behavioural disturbances like hyperactivity, attention deficit, and affective disorders. This may have long-term educational, social and financial implications.

There are several difficulties extrapolating animal data to human children:
- Synaptogenesis occurs over a far longer period in humans than in rats, giving a broad window of vulnerability. A child would therefore be exposed to anaesthetic drugs for a minute fraction of the “at-risk” period.
- The rats and primates studied were exposed to anaesthesia without noxious stimuli (pain/surgery). Painful stimuli themselves activate NMDA- and other excitatory receptors in the immature brain; therapeutic doses of anaesthetic drugs will thus protect the brain from these effects.
- The animals studied were not continuously monitored for haemodynamic stability, or for evidence of hypoxia or hypercarbia. These variables are continuously monitored intraoperatively in paediatric anaesthetic practice.
- The doses and duration of the anaesthetic drugs given can’t be shown to correlate with those used in humans.

To date, there are no prospective trials regarding neurodevelopmental outcomes after exposure to anaesthesia in children.

There are five retrospective cohort studies in the literature, with conflicting results.

Wilder et al studied the association between anaesthetic exposure before the age of four and the development of learning disabilities,’ as mentioned earlier.

There are several limitations to this study. The anaesthetics were administered before the routine use of pulse oximetry and capnography were made mandatory by the ASA, making it impossible to exclude intraoperative complications such as hypoxia as a causal factor for LD. The researchers can’t exclude that the LD was causally linked to pre-existing comorbidities (such as obstructive sleep apnoea) or the indication for surgery (for example, chronic serous otitis media).

N₂O was used in 91% of the anaesthetics, halothane in 88%, and ketamine in 9%. This may mean that their results cannot be extrapolated to current practice.

Sprung et al studied a cohort of 5 320 children to determine the neurocognitive effects of perinatal exposure to anaesthetics during labour and delivery. They found that children exposed to general o regional anaesthesia during Caesarean section are not more likely to develop LD compared to children delivered vaginally without regional anaesthesia, suggesting that brief perinatal exposure to anaesthetic drugs does not adversely affect long-term neurodevelopmental outcomes.

Di Maggio et al reported that children having anaesthesia and surgery for 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 behavioural disorder.

They acknowledge that children having hernia repair are more likely to have a “potentially confounding diagnosis” such as low birth weight, perinatal hypoxia, or congenital anomalies. They do not comment on how many of the children in each group were born prematurely, a condition that is associated with a high incidence of inguinal hernias. Nonetheless, their statistically significant results have been seen as a cause for concern.

Kalkman et al performed a survey of long-term behaviour after childhood urologic surgery. Their study was based on parental responses to a questionnaire, and showed that children who had surgery before two years old were more likely to show “deviant” behaviour than those operated on after two years, but these results were not statistically significant. There was no control group.

A twin study from the Netherlands that looked at data from 1 143 monozygotic twin pairs showed no evidence for a causal relationship between anaesthesia and LD.

**Is it anaesthesia that causes the problem?**

There are confounding variables in all the research studies. Perinatal brain injury and subsequent...
neurodevelopmental delay and disability are likely multifactorial:

- Prenatal exposure to alcohol, tobacco, cocaine and pesticides have all been associated with neurobehavioural deficits.
- Thirty per cent of infants with congenital heart disease may have widespread brain abnormalities before undergoing surgery. During surgery, both deep hypothermic cardiac arrest and low haematocrit on bypass are associated with later neurologic dysfunction.
- Premature infants are more likely to have poor neurodevelopmental outcomes, especially those with extremely low birth weights, neonatal infections, necrotising enterocolitis, or bronchopulmonary dysplasia.
- Malnourished children are at risk.
- In older children, chronic disease states (such as renal failure requiring long-term dialysis), chronic pain, and frequent hospitalisation all affect psychological development. These children may have delayed cognitive and academic development, and are also more likely to be anxious, depressed and aggressive. These effects have not been shown to be increased or aggravated by repeat exposure to anaesthesia, as long as perioperative pain and anxiety are well managed.
- Behavioural abnormalities may occur in up to 50% of children after surgery and anaesthesia. These include clinginess, bed-wetting, and sleep disturbance. Most cases settle within a month to a year, and no long-term behavioural problems have been documented. Risk factors include younger patient age, severe postoperative pain, and lack of sedation prior to induction.
- We should also remember that the nervous system continues to remodel and change throughout development and into adulthood. Neuroplasticity may allow for repair to lesions sustained by the developing brain.

Do children need anaesthesia?

Physiological pain pathways are present by 25 weeks. Apart from raising ethical concerns, surgery without anaesthesia induces long-term changes in pain processing, hyperalgesia, and a variety of neurodevelopmental, behavioural and cognitive deficits.

There are also numerous settings in which anaesthesia has been shown to be protective, such as on cardiopulmonary bypass, especially during deep hypothermic cardiac arrest and during periods of decreased CMRO₂ (cerebral metabolic rate of oxygen).

The way forward

Large multi-centre prospective studies are underway. These include the GAS (GA vs Spinal) study, assessing infants undergoing hernia repair, and the Pediatric Anesthesia and Neuro Developmental Assessment (PANDA) study, which is a cohort study enrolling 500 sibling pairs. The results of these studies will only be available in five years or more.

Until we have answers, the following seem to be sensible recommendations:

- Delay truly elective surgery until six to 12 months of age.
- Maintain haemodynamic stability and avoid hypoxia and hyper- or hypocapnia.
- Avoid the combination of NMDA-antagonists and GABA-agonists, including nitrous oxide.
- Use appropriate doses of anaesthetic agents.
- Prevent pain.
- Consider the use of regional anaesthetic techniques where possible.
- Consider high-dose synthetic opiate techniques for major thoracic or abdominal procedures.

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