The rise and fall of anaesthesia-related neurotoxicity and the immature developing *human* brain

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Very few issues (if any) within paediatric anaesthesia have, during the past roughly 15 years, caused so much concern and emotional disturbances as a plethora of animal studies that repeatedly have shown that exposure to most of the currently used anaesthetics during a vulnerable period of brain development (i.e. brain growth spurt or peak of synaptogenesis) may possibly lead to neurodegeneration (particularly apoptosis) and abnormal synaptic development.[1–4] Importantly, the observed morphological abnormalities are associated with functional deficits in learning and behaviour later in life. Initial studies were mainly performed in immature rodent pups, but more recent studies have included non-human primates.[5–7] Given the number of neonates, infants and young children anaesthetized annually worldwide, these findings could have significant public health implications.

This has obviously raised concern in the paediatric anaesthetic community about the potential effects in human babies that are exposed to anaesthesia in early life and the anxiety level has increased further, mainly in the USA,[8–11] where debatable epidemiologic studies (single-centre studies, small samples sizes, inclusion of multiple surgeries, migration problems, multiple and interrelated outcomes, large age span with few neonates and infants) point to similar long-term effects in children that have been exposed to anaesthesia during infancy.[12–21]

Hence, all the above has resulted in position statements from various societies and governmental bodies regarding anaesthesia in early life[8–11] and very substantial NIH grant money has been allocated to further research within this field.

Fortunately, much more robust, large-scale and nationwide epidemiologic studies from Europe (mainly the Netherlands, Denmark and most recently Sweden)[22–25] have failed to find any relevant negative effects of anaesthetic exposure in young children. There are also a number of fundamental issues that challenge the individuals or the research groups that are on an "Apoptosis crusade":

The original animal studies on anaesthesia-related neurotoxicity and the developing brain were never driven by any clear-cut or well-defined associations between exposure to general anaesthesia and subsequent specific neurocognitive deficits in human infants.[3,26] Rather, the pressure was driven by established (animal) research areas focusing on the foetal alcohol syndrome and long-term exposure to certain anti-epileptic drugs. Hence, given the anticipated (but unknown) mechanisms of actions behind these conditions or relationships it was deemed likely to expect that anaesthetic drugs

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may also produce neuronal damage in similar experimental settings. Indeed, this immediately was shown to be the case, and resulted in numerous publications (mainly pre-clinical, review and commentary) and academic positions related to the topic, because real translational conclusions are impossible to attain.

However, we would advise people to relax because if it really was that harmful to be anaesthetized in early life, we would most likely have suspected this phenomenon ages ago.[26,27]

Translating these animal studies into a human clinical context is obviously difficult. How do various developmental stages of brain development in animal models translate into humans? The anaesthetic techniques and managements used in the majority of animal (rodent) studies are extremely different to normal clinical practice, i.e. the use of supra-clinical doses and long duration of exposure to anaesthetic drugs sometimes resulting in excessively high mortality (20–80%). Additionally, the use of multiparameter monitoring and control of airway and respiration are difficult (or even impossible) due to the small size of the immature animal pups, which also precludes repeated blood gas and glucose measurements due to small circulating blood volumes.[3,26] This may be of utmost importance. A recent animal study by Wu et al. compared the effects of mechanical ventilation and spontaneous breathing on outcome in 14-day-old rats exposed to isoflurane and sevoflurane. Compared with mechanical ventilated rats, spontaneous breathing rats had significantly higher mortality, neuroapoptosis and impaired neurocognitive outcome.[28]

Furthermore, recent rodent studies have shown that if immature neonatal rodents are exposed to "an enriched environment", i.e. were allowed access to mothers and "toys" in their cage, instead of an environment of sensory deprivation, it is no longer possible to reproduce any negative long-term effects.[7]

The majority of studies have used rodent pups at post-natal day 7 (PD7) as this is the optimal time to detect increased apoptosis in the most susceptible parts of the brain (e.g. stria terminalis, olfactory bulb). This is of cause the right time if you wish to provoke apoptosis in this context. However, PD7 corresponds to anaesthetic exposure of an extremely premature child and not to the major target population of term babies and young infants where PD10-14 is much more appropriate.[29] The ability to show increased apoptosis at PD7 is therefore of doubtful value (for more details www.translating-time.net).

Many of us have experienced children coming back for follow-up CT or MRI scans due to substantial intracranial haemorrhage in the neonatal period or some other major cerebral insult at an early age. In a number of these children more or less an entire hemisphere is "missing" or significantly damaged, yet it is very difficult clinically to detect this. Thus, the human brain has a tremendous and phenomenal potential for neural plasticity and compensation after major cerebral insults in early life. Considering the fact that the fraction of brain cells that undergo enhanced (×5–40) programmed cell death in these studies in fact is less than 0.1% of the total number of cerebral neurons[30] it seems very unlikely that this tiny and discrete extra loss of brain cells should be associated with any long-term effects later in life.

Despite the inherent differences in the above-mentioned cohort studies, why are there such striking differences between the epidemiologic studies from North America and the epidemiologic studies generated (mainly) in Europe? Private/insurance based health care vs. mainly national health care systems with access for everyone? Differences in the access to and quality of the school systems between the continents? Or rather a desperate desire to keep and expand the NIH funding for the research group?

Regardless of everything above, neonates and infants require and need important surgical interventions to be performed without delay, and do for both humanitarian and medical reasons need high-qualitative anaesthetic care despite any minor consequences this may or may not have later in life.

Meanwhile, the first reports of prospective trials are emerging. The recent 2-year interim analysis of the GAS study reports that sevoflurane exposure of up to 1 h in infancy (up to 60 weeks post-conceptual age) does not increase the risk of adverse neurodevelopmental outcome.[31] Even if this is considered only as a secondary outcome of this very important large prospective randomized clinical trial it is consis-

tent with the largest cohort studies published so far as well as the most recent infant primate data who underwent rigorously controlled sevoflurane anaesthesia and subsequent housing within their natural surroundings and nurtured by their mothers.[7] Moreover, when the primary neurocognitive outcome measure of the GAS study is analysed 3 years from now (when the children are age 5 years) the results will most likely be similar. This does not imply that anaesthesia is "safe" in young children, because these results cannot be extrapolated to longer and multiple anaesthetics and extremely premature infants. However, it will be very difficult to get any scientific proof of longer anaesthetics and almost impossible to get proof regarding multiple anaesthetic exposures (RCTs will be complicated to perform; time consuming, laborious and the numbers will be too small). It seems more sensible to focus on all the other factors[32–34] that affect outcomes in young perioperative children (www.safetots.org). Maybe the skill and dedication of the anaesthetist is much more important than what drugs are being used?[35]

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