Neurodevelopment after general anaesthesia in infants

Concerns about anaesthesia-related neurological injury in young children have been increasing among parents, health-care providers, and regulatory organisations. These concerns were first prompted by animal studies that showed accelerated apoptosis and neuronal death after exposure to general anaesthetic drugs.1 Most commonly used general anaesthetic drugs have since been found to cause pervasive adverse neurological effects in vitro and in immature animals, including non-human primates.2 This issue gained widespread prominence in 2017, when the US Food and Drug Administration issued a safety communication stating that the use of general anaesthetic drugs “for lengthy periods of time or over multiple surgeries or procedures may negatively affect brain development in children younger than 3 years”.3 Subsequently, warnings were added to the labels for these medicines.

Interpreting the clinical relevance of anaesthesia-related neurological injury has been challenging and controversial, especially given the difficulties of translating findings from animal studies to humans.4 Clinical studies to date have been restricted to observational cohorts, which have many inherent limitations, and their findings have been mixed.5 What have been sorely missing are definitive clinical studies providing high-quality evidence of a relationship between exposure to anaesthesia and neurological injury. This information is essential to guide treatment decisions for children who are scheduled to undergo general anaesthesia.

In The Lancet, Mary McCann and colleagues6 present the results of the GAS study, the first randomised controlled trial, to our knowledge, to investigate whether exposure to general anaesthesia in young children adversely affects longer-term neurodevelopmental outcomes as compared with awake-regional anaesthesia. This equivalence trial included patients from 28 hospitals in seven countries. Infants younger than 60 weeks’ postmenstrual age who required repair of an inguinal hernia were randomly assigned to undergo either an awake-regional anaesthetic technique (spinal, caudal, or combined caudal and spinal anaesthetic; n=361) or a general anaesthetic technique (with inhaled sevoflurane; n=358). The primary outcome was the Wechsler Preschool and Primary Scale of Intelligence Full Scale Intelligent Quotient (FSIQ), measured at 5 years of age. The median duration of general anaesthesia was 54 min (IQR 41–70). The adjusted mean difference in FSIQ for awake-regional minus general anaesthesia was 0·16 (95% CI –2·45 to 2·78) in the intention-to-treat analysis and 0·23 (95% CI –2·59 to 3·06) in the per-protocol analysis (69 [19%] of 361 infants in the awake-regional group were also exposed to general anaesthesia). There were no significant differences in a range of secondary neurocognitive and behavioural outcomes.

A previous analysis of the GAS study using shorter-term secondary outcomes measured after 2 years of follow-up also showed equivalence between awake-regional and general anaesthesia.7 The current and final study results (measured at age 5 years) should strongly reassure health-care professionals that general anaesthesia lasting just less than 1 h in young children does not adversely affect long-term neurodevelopmental outcomes. The scientific rigour and conduct of the trial were exemplary, and intelligence testing at this older age has strong predictive potential for future achievement.

Despite being anticipated in the study design, there was greater-than-expected loss to follow-up during the 5 years, resulting in incomplete data for some participants (complete case data were available for 447 of 719 participants). Multiple imputation was used to deal with the missing data, and the precision of the results is supported by the CIs, which fall within the pre-specified bounds of equivalence (a difference of 5 FSIQ points). Adverse neurodevelopment in childhood results from interactions among multiple risk and protective factors, including health-care-related, genetic, familial, and environmental factors. Consequently, potential contributing factors other than general anaesthesia (eg, type of surgery, sex [84% of study participants were male]) should be considered when interpreting and generalising these findings. Perhaps most importantly, the study results cannot be extrapolated to children who undergo prolonged or repeated exposures to general anaesthesia or receive multiple anaesthetic drugs for the same surgical procedure.

The study results are consistent with the literature. Preclinical studies predominantly support a dose-response relationship between the duration of general anaesthesia and adverse cellular and functional outcomes.8 Additionally, several observational studies
have reported no long-term deficits in FSIQ in children who were exposed to a single general anaesthetic at a young age (<3 years).3,20

The GAS study provides the strongest evidence to date that a single, brief (less than 1 h) exposure to general anaesthesia during infancy is not harmful to gross neurodevelopment. Preclinical studies, however, provide a clear signal that neurological injury can occur after lengthy or repeated exposures. Whether anaesthesia causes neurological injury in patients under these conditions remains to be established. Clarifying the dose-dependence of anaesthesia-related neurotoxicity will require careful experimental design and will best be tackled through a consensus-based, clearly defined research agenda for both preclinical and clinical studies. Fortunately, as evidenced by the GAS study, the anaesthesia research community has the ability to effectively collaborate to address these challenging questions.

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Improving survival in molecularly selected glioblastoma

Clinical investigation of novel treatments for glioblastoma has been met with repeated setbacks over the past two decades. Modest, but clinically meaningful, improvement in survival has only been shown for temozolomide1 and tumour-treating fields,5 whereas many randomised trials assessing drugs targeted to vascular endothelial growth factor,4 integrins,5 and epidermal growth factor receptor (EGFR),6 showed that such drugs failed to prolong patient survival.

Overcoming the treatment resistance mediated by O-6-methylguanine-DNA methyltransferase (MGMT), a DNA repair protein that has a key role in reversing some DNA damage induced by alkylating agent chemotherapy, such as temozolomide, is of interest. Trials7 aiming at competitively inhibiting MGMT with chemotherapy, such as temozolomide, is of interest. Trials2 aiming at competitively inhibiting MGMT with 6-benzyl guanine were associated with toxic effects that required substantial dose reductions. Because MGMT is consumed when repairing DNA, exhausting MGMT reservoirs by a dose-intensive and continuous temozolomide administration was another rational strategy that ultimately did not translate into any clinical benefit in a large randomised trial. Studies4 have shown that MGMT promoter methylation—leading to gene silencing and absence of expression of the associated MGMT repair protein—is a strong predictive marker for benefit from nitrosourea and temozolomide chemotherapy. Therefore, restricting alkylating agent chemotherapy to patients with a methylated MGMT promoter is a rational strategy, allowing the treatment to be targeted to a population that is more likely to benefit from the intervention.8 However, the choice of an adequate cutoff in the respective MGMT assays and validation with outcome is not trivial.

In The Lancet, Ulrich Herrlinger and colleagues10 report the results of a phase 3 trial comparing a combination of the two drugs with the best track record in glioma, lomustine and temozolomide, with standard concomitant chemoradiotherapy followed by adjuvant temozolomide. Although a total of 653 patients with newly diagnosed glioblastoma...