



## Editorial

# Neurotoxicity of anaesthetics on developing brain: a relevant question or just a “bias”?



## ARTICLE INFO

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Despite the number of studies performed in the era of the neurotoxicity of anaesthetic agents on the developing brain, studies are still exhibiting conflicting results especially when focusing on those evaluating cognitive functions. Some of those studies have shown cognitive functions to decline following general anaesthesia.

### 1. Recent conflicting results in the clinical field

Two Australian studies performed on the same birth cohort (the Western Australian Pregnancy Cohort) have shown that:

- infants operated before the age of 3 years exhibit long-lasting lower cognitive functions [1] and;
- that a duration of exposure to anaesthesia lower than 35 minutes was not associated with any cognitive decline [2].

In contrast, other studies have not found such an association; this is the case of the study performed by Glatz et al. on more than 33,000 children operated before the age of 4 years [3] or the PANDA study [4] which compared twins to their brother or sister, respectively. Finally, the Kindergarten Canadian cohort [5] found no association between exposure to anaesthesia before the age of 2 years and alteration in cognitive functions, while such an association was found when children were operated between 2 and 4 years. Recently, the controlled GAS study has come to confirm the absence of effect of general anaesthesia on cognitive functions after a short and single exposure to anaesthesia [6]. Randomising patients younger than 60 weeks of post-conceptional age undergoing hernia repair surgery to either general or regional anaesthesia, Davidson et al. found no evidence of cognitive decline in those patients submitted to general anaesthesia. The definitive results of the study will be available at 5 years of follow-up, but given that no tendency has been observed at 2 years, the probability of any observed effect at 5 years seems very small. Another important particularity of the

GAS trial is the short duration between the exposure to anaesthesia and the cognitive evaluation (2 years), which differs with most studies that assessed outcomes on average 10 years later.

The result of the study published by Khochfe et al. [7] in this issue of *Anaesthesia Intensive Care and Pain Medicine* found patients undergoing hernia repair before the age of 2 years under general anaesthesia to exhibit a greater proportion of patients with cognitive decline 10 years later in comparison with patients operated under spinal anaesthesia. Although, the study was not randomised, it was adequately powered according to the primary outcome (cognitive functions according to the Eyberg Child Behavior Inventory). In addition, durations of interventions were longer in comparison to the GAS trial, which includes surgeries of duration < 60 minutes. Those results are surprising but might be explained by many factors.

### 2. Confounding factors: Influence of the social and familial environment

Considering the current literature based on large cohorts (i.e. excluding the GAS trial): all are not randomised and even if results have been adjusted to many covariates, especially those related to birth conditions and social environment such as parental education level, there is no guarantee that results are not impacted by unstudied internal or external factors. This is accredited by large cohorts, especially the British birth cohort (the seventies one) that found that, for instance, family environment and education at 5 years old can predict long term quality of life thirty years later [8]! Moreover, many studies both in humans and animals have shown life events to affect many brain structures [9,10]. As an example, studying young men (between 18 and 21 years old) submitted to early adversity during the first 6 years of life, Jensen et al. [11] found those persons to exhibit structural modifications in many brain regions including the anterior cingulate cortex and the precuneus. One can also hypothesise that a major and stressful event, such as a surgical intervention, might also impact the neurological development in children, especially when repeated and/or associated with psychological stress in family members.

### 3. Confounding factors: factors related to the surgical procedure

Another important factor to consider for our practice is the development in anaesthesia techniques over times. Recent

advances in the management of children during anaesthesia with the definition of hypotension have decreased the occurrence of occult hypoperfusion events during anaesthesia and risks of subclinical episodes of brain ischaemia [12,13]. This might be the main difference between the GAS trial that controlled this important factor and all other previous non-controlled studies (including the present one). This hypothesis is supported by the fact that spinal anaesthesia is haemodynamically well tolerated in infant [14] and could be related to the time-dependant effect of general anaesthesia on learning and cognitive function found in some studies [2,15]. Indeed, one can easily hypothesise that increasing the duration of anaesthesia will increase the duration of exposure to anaesthetic agents but also the risk of developing hypotension or other cerebral aggression.

#### 4. Conclusion

The problem of the neurotoxicity of anaesthesia agents might rather be a problem of practice of anaesthesia. Accordingly, physicians should focus on respecting recommendations concerning maintaining both intraoperative arterial pressure, adequate ventilation, avoiding both hyper and hypocapnia and preventing anxiety. Otherwise, family, social environment and life events might be major determinants of brain development and long-term cognitive functions. ... and anaesthesia and surgery just one event among many others [16].

#### Disclosure of interest

The authors declare that they have no competing interest.

#### References

- [1] Ing C, DiMaggio C, Whitehouse A, Hegarty MK, Brady J, von Ungern-Sternberg BS, et al. Long-term differences in language and cognitive function after childhood exposure to anesthesia. *Pediatrics* 2012;130(3):e476–85.
- [2] Ing C, Hegarty MK, Perkins JW, Whitehouse AJO, DiMaggio CJ, Sun M, et al. Duration of general anaesthetic exposure in early childhood and long-term language and cognitive ability. *Br J Anaesth* 2017;119(3):532–40.
- [3] Glatz P, Sandin RH, Pedersen NL, Bonamy A-K, Eriksson LI, Granath F. Association of Anesthesia and Surgery During Childhood With Long-term Academic Performance. *JAMA Pediatr* 2017;171(1):e163470.
- [4] Sun LS, Li G, Miller TLK, Salorio C, Byrne MW, Bellinger DC, et al. Association between a single general anesthesia exposure before age 36 months and neurocognitive outcomes in later childhood. *JAMA* 2016;315(21):2312–20.
- [5] Graham MR, Brownell M, Chateau DG, Dragan RD, Burchill C, Fransoo RR. Neurodevelopmental assessment in kindergarten in children exposed to general anesthesia before the age of 4 years: a retrospective matched cohort study. *Anesthesiology* 2016;125(4):667–77.
- [6] Davidson AJ, Disma N, de Graaff JC, Withington DE, Dorris L, Bell G, et al. Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial. *Lancet* 2016;387(10015):239–50.
- [7] Khochfe AR, El Rajab M, Ziade F, Naja Z, Naja A, Naja Z. The effect of regional anesthesia versus general anesthesia on behavioral functions in children. *Anaesth Crit Care Pain Med* 2018. <http://dx.doi.org/10.1016/j.accpm.2018.03.012> [pii: S2352-5568(17)30305-3; Epub ahead of print].
- [8] Layard R, Clark AE, Cornaglia F, Powdthavee N, Vernoit J. What predicts a successful life? A life-course model of well-being. *Econ J (London)* 2014;124(580):F720–38.
- [9] Lupien SJ, Juster R-P, Raymond C, Marin M-F. The effects of chronic stress on the human brain: From neurotoxicity, to vulnerability, to opportunity. *Front Neuroendocrinol* 2018.
- [10] Christoffel DJ, Golden SA, Russo SJ. Structural and synaptic plasticity in stress-related disorders. *Rev Neurosci* 2011;22(5):535–49.
- [11] Jensen SKG, Dickie EW, Schwartz DH, Evans CJ, Dumontheil I, Paus T, et al. Effect of early adversity and childhood internalizing symptoms on brain structure in young men. *JAMA Pediatr* 2015;169(10):938–46.
- [12] De Graaff JC, Pasma W, van Buuren S, Duijghuisen JJ, Nafiu OO, Kheterpal S, et al. Reference values for non-invasive blood pressure in children during anesthesia: a multicentered retrospective observational cohort study. *Anesthesiology* 2016;125(5):904–13.
- [13] Michelet D, Arslan O, Hilly J, Mangalsuren N, Brasher C, Grace R, et al. Intraoperative changes in blood pressure associated with cerebral desaturation in infants. *Paediatr Anaesth* 2015;25(7):681–8.
- [14] McCann ME, Withington DE, Arnup SJ, Davidson AJ, Disma N, Frawley G, et al. Differences in blood pressure in infants after general anaesthesia compared to awake regional anaesthesia (GAS Study-A Prospective Randomized Trial). *Anesth Analg* 2017;125(3):837–45.
- [15] Wilder RT, Flick RP, Sprung J, Katusic SK, Barbaresi WJ, Mickelson C, et al. Early exposure to anesthesia and learning disabilities in a population-based birth cohort. *Anesthesiology* 2009;110(4):796–804.
- [16] McEwen BS. Protective and damaging effects of stress mediators. *N Engl J Med* 1998;338(3):171–9.

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