Title: Early anesthesia exposure and the effect on visual acuity, refractive error and retinal nerve fiber layer thickness of young adults

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ABSTRACT

Objective: To investigate whether being anesthetized at least once in early life had an impact on three main proxies of visual function: visual acuity (VA), refractive error (RE) and optic nerve health in young adulthood.

Study Design: At age 20 years, participants of Western Australian Pregnancy (Raine) Cohort had comprehensive ocular examinations including VA, post-cycloplegic refraction and multiple scans of the optic disc. We identified individuals who had at least one procedure requiring anesthesia during the first 3 years of life (between 1990 and 1994) and compared their visual outcomes with non-exposed individuals. We excluded 40 participants with strabismus or other ophthalmic disease or surgery and 136 with non-European background.

Results: 15.2% of 834 participants (n=127) were exposed to anesthesia at least once before age 3 years. In both exposed and non-exposed groups, median VA was -0.06 logMAR in the right eye and -0.08 logMAR in the left eye ($p>0.05$). Median spherical equivalent RE was +0.44 D (interquartile range [IQR]: -0.25, +0.63) and +0.31 D (IQR: -0.38, +0.63) in the exposed and non-exposed group respectively ($p = 0.126$). No difference was detected in mean global retinal nerve fiber layer (RNFL) thickness of the two groups (100.7 μm vs 100.1 μm , $p=0.830$).

Conclusion: We were unable to demonstrate an association of exposure to anesthesia as a child with reduced VA or increased myopia or thinning RNFL. Although this supports the view that anesthesia is unlikely to impair visual development, further work needs to be done to establish whether more subtle defects are present and repeated exposures have any effects.

INTRODUCTION

“Primum non nocere – first do no harm” is the overriding principle in medicine. Yet, the crucial question of whether being anesthetized as a child harms brain development remains largely unanswered. While some studies showed children had an increased risk of being diagnosed with subsequent cognitive impairment following anesthesia exposure in early childhood¹⁻⁵, others found no evidence for a neurotoxic effect of a single anesthesia exposure.⁶⁻⁸ However, there is some consistent evidence suggesting that repeated anesthesia exposure is related to cognitive deficit later in life.^{2,9-11}

In the human brain, age-related synaptogenesis in the visual cortex (V1) begins during gestation and progresses in two stages. The first period, which ends at about postnatal age 8 months, involves rapid synapse production whilst the second is a longer period of synapse elimination that extends past age 3 years. The experience-dependent cortical plasticity studies allowed us to understand that uncorrected firing of action potentials between the pre-synaptic and post-synaptic neurons in V1 weakens synaptic connections.¹² These excitatory synaptic transmissions are mainly mediated by NMDA and 5-methyl-4-isoxazolepropionic acid (AMPA) receptors while inhibitory synaptic transmissions are regulated by GABA_{Aα} receptors.^{13,14} Recently, Hensch and colleagues demonstrated that increasing inhibition throughout the critical period with GABA_A receptor agonists could lead to a 30% increase in columnar width of the visual cortex whereas inverse agonists could produce column shrinkage.¹⁵

Due to the aforementioned neuronal activities occurring during visual development in humans and the evidence for cognitive impairment in individuals exposed to anesthesia, we hypothesized that exposure to these agents in early childhood could potentially impact

normal visual development. Standard synaptogenesis in a child's brain continues until the end of teen years and the visual system is not completely developed and refractive status is not stabilized until early adulthood. This study was set out to investigate whether being anesthetized at least once during early life had an impact on three surrogate measures of visual function; these being visual acuity, refractive error and thickness of retinal nerve fiber layer (RNFL) in young adulthood.

METHODS

The Western Australian Pregnancy Cohort (Raine) Study is an ongoing prospective cohort study of pregnancy, childhood, adolescence and young adulthood in Perth, Western Australia. At the initiation of the study, 2900 pregnant women at 16-18 weeks' gestation were recruited from the state's largest public women's hospital and surrounding private practices for a randomized clinical trial investigating effects of intensive ultrasound imaging and Doppler flow studies in pregnancy outcomes¹⁶.

Following this study, 2868 offspring born to 2804 of the recruited women have been evaluated in detail during subsequent childhood, adolescent and young adult follow-ups. From birth, parents were asked to keep detailed diaries of their child(ren)'s medical history. At the 1-, 2- and 3-year follow-ups, parents were asked to complete questionnaires describing illnesses and medical problems, which were then coded into the International Classification of Diseases (9th Revision) by the research staff. Any child who had a surgical or diagnostic procedure requiring anesthesia before the age of 3 years was classified into the "exposed" group. The remaining individuals were included in the "non-exposed" group. Exposure to anesthesia was confirmed by review of the types of procedures recorded in the questionnaire. Individuals who were found to have diagnostic procedures not requiring anesthesia were

classified into the non-exposed group. No direct access was available to medical records perinatally including surgical and anesthetic records.

At the 20-year review of the cohort, participants underwent a comprehensive ocular examination. This examination included assessments of best-corrected visual acuity using LogMAR chart and contrast sensitivity (CS) using a low-contrast letter chart (Test Chart Xpert, Thomson Software Solutions, UK), measurement of refractive error by autorefraction (Nidek 510 ARK, NIDEK Co. Ltd, Japan) after administration of cycloplegic drops and an orthoptic examination by a qualified orthoptist. Refractive error was determined as spherical equivalence (SE) by summing the spherical error and half the cylindrical error. During the examination, ocular history including previous ocular surgery and/or diagnostic procedure was recorded and binocular vision function was assessed. Those who were reported to have strabismus surgery as a child were excluded from the analysis. RNFL thickness measured both globally and in four quadrants around the optic disc using Spectralis spectral-domain optical coherence tomography (Heidelberg Engineering GmbH, Heidelberg, Germany). Unclear scans or scans with low signal strength were removed from the dataset.

The 20-year follow-up of the Raine Study cohort obtained ethics approval from the Human Research Ethics Committee at the University of Western Australia. The study was conducted in accordance with the Declaration of Helsinki and informed consent was obtained from all participants. Previous ethics approvals were completed for each of the earlier examinations.

Statistical Analysis

All variables were assessed for normality and summarized using median (interquartile range [IQR]). Differences between two continuous variables were assessed with the Mann-Whitney

U test. Differences between categorical variables were assessed with the chi-squared test. We used mean SE refractive error of both eyes to estimate the prevalence of myopia. Myopia was defined as mean SE refractive error < -0.5 diopters (D). Statistical analyses were considered significant at the $p < 0.05$ level and all P -values were two-tailed. Statistical analyses were performed using the statistical software R version 2.15.1 (R Foundation for Statistical Computing; <http://www.r-project.org/>).

RESULTS

Ophthalmic and pediatric anesthesia exposure data were available for 1010 individuals. We excluded 8 individuals who were reported to have strabismus surgery in early life questionnaires and 32 individuals identified with strabismus and other ocular problems at the time of eye examinations. 136 individuals with non-European ancestry had more myopic refractive error compared to their peers with Northern European ancestry (median SE of $+0.12$ vs $+0.31$ diopters, $p < 0.001$), thus they were excluded from the analysis (Figure 1). No participants had a history of an ophthalmic disease diagnosis other than strabismus that required surgery in the first 3 years of life.

Of the 834 individuals included in the analysis, 420 (51.3%) were male and the mean age of the participants at ocular examination was 20.0 ± 0.42 years (range: 18.3 to 22.1). 127 (15.2%) participants were exposed to anesthesia at least once before the age of 3 years. While 24 individuals exposed to anesthesia twice, only 9 individuals had three or more exposures. No age difference was present between the exposed and non-exposed groups ($p=0.99$); however, there were more boys in the exposed group compared to non-exposed group (63.0% vs 49.4% males, $p=0.005$).

28 participants (3.1%) had a score of less than 80 seconds of arc indicating reduced binocularity. Of those, 24 did not have exposure to anesthesia in the first 3 years of life. None of participants had amblyopia that is defined as two lines of visual acuity difference. Table 1 displays the comparison of exposed versus non-exposed group results for visual acuity and refractive error. Median visual acuity was -0.06 logMAR score in the right eye and -0.08 logMAR score in the left eye of the exposed group. No difference was present in visual acuity of both exposed and non-exposed groups ($p_{\text{right eye}} = 0.625$ and $p_{\text{left eye}} = 0.413$). Similarly, there was no difference in contrast sensitivity of the two groups (median CS in both eyes for both groups = 1.35 logCS, $p > 0.05$). The median SE refractive error of both eyes was +0.44 D (IQR: -0.38, +0.75) in the exposed group and +0.31 D (-0.25, +0.63) in the non-exposed group ($p = 0.126$). 18.4% of the exposed group were myopic compared to 19.7% of the non-exposed group ($p = 0.729$).

The mean global RNFL thickness was $101.1 \mu\text{m} \pm 13.3$ in the exposed group and $100.8 \mu\text{m} \pm 10.9$ in the non-exposed group ($p = 0.830$). As displayed in Table 2, there was also no difference in mean RNFL thickness in any of the quadrants between the two groups.

DISCUSSION

The results of this study suggest that exposure to anesthesia in early childhood is not associated with reduced visual acuity or increased myopia in young adulthood. Previously, it was shown that the offspring of mothers who were exposed to anesthesia during pregnancy exhibited longer “looking times” at the visual stimuli and had different visual pattern preferences compared to an unexposed control group.¹⁷ We compared best-corrected visual acuity of the individuals who were exposed to anesthesia early in life and found no difference compared to their non-exposed peers. Visual acuity is an outcome from the proper

functioning of the cornea, lens, retina, optic nerve (axon and myelination) and higher cortical aspects from parietal/temporal/occipital lobe; however, the term 'vision' has broader applications highly dependent on higher cortical functioning (proprioception, movement, color, face/letter/object recognition) that can be dysfunctional despite a normal visual acuity. For example, a patient with temporal-occipital lobe injuries can have normal visual acuity but 'poor vision'. For this reason, although visual acuity cannot be generalized to visual development and vision completely, it is a strong surrogate that measures the development of various structures within the visual pathway. It is therefore likely that the evidence of no association between the visual acuity and anesthesia exposure may also account for the hypothesis that early anesthesia has no effect on vision.

Emmetropisation of the eye highly correlates with the eye growth and is mediated by a local feedback loop within the sensory retina¹⁸ without involvement of the central nervous system (CNS). Some evidence suggests that through involvement of various amacrine cells, via the choroid and sclera, the CNS could have at least a modulatory influence on eye growth and emmetropisation.^{18,19} Moreover disconnecting the eye from the CNS by cutting the optic nerve alters the regulatory process in chick models, suggesting that an intact optic nerve and healthy CNS appear to be essential for emmetropia and normal eye growth.²⁰ Deprivation of vision due uncorrected myopia, cataracts and corneal dystrophy can be associated with poor emmetropisation in children. Kugelberg et al.²¹ found children with unilateral congenital cataract have shorter axial length in the affected eye compared to unaffected eye. Despite these evidence, similar to visual acuity, no difference was present in refractive error of the exposed and non-exposed groups.

During normal synaptogenesis, a small percentage of neurons (<1%) that are redundant are eliminated through apoptosis.²² Yet it was surprising when Ikonomidou and colleagues²³ first reported that blockade of glutamate *N-methyl-d-aspartate* (NMDA) receptors, or the excessive activation of γ -aminobutyric acid (GABA_A) receptors could result in apoptotic neuronal degeneration in developing rat brains particularly during synaptogenesis. Retinal ganglion cells (RGCs) are the last chain of the neurons that link the eye to the brain. Given that RNFL axons originates from the RGC bodies, we postulated that a possible reduction in RNFL thickness may indicate RGC loss in young adults who were exposed to anesthesia early in life. However, our findings did not support this hypothesis.

The generalizability of these results is subject to certain limitations. The outcomes we studied were secondary measures for the cohort study, and that the sample size might be lacking. Moreover, our data were underpowered to investigate the effect of repeated measures on visual acuity, refractive error and RNFL thickness. Due to lack of access to medical records, we were unable to identify the anesthetic agents used and the dosage and duration of the anesthesia. During the period when the Raine Study participants were exposed to anesthesia (1990-1994), there was likely initially a predominance of halothane and enflurane followed by increasing numbers of patients receiving isoflurane or sevoflurane.⁴ Halothane depresses the CNS by blocking the effects of the excitatory neurotransmitter, glutamic acid, at the NMDA receptors. Similar to the neurotoxic effects caused by other inhalation anesthetic agents, significant reduction in synaptic density was observed in rat models after chronic exposure to halothane.^{24,25} It must be noted that some of the anesthetic agents such as halothane and enflurane are no longer widely used and may have greater neurotoxic effects than the agents used currently. Also, we were unable to eliminate all other illness and surgeries that may have affected visual acuity and other measures from early childhood to

young adulthood. Finally, results of this study are limited to individuals with Northern European ancestry.

In conclusion, despite evidence for adverse effects of anesthesia on the developing brain, our findings suggest that exposure to anesthesia at least once in early childhood likely has no impact on three important proxies of visual function: visual acuity, refractive error and RNFL thinning. To our knowledge, this is the first clinical study reporting evidence from a longitudinal study of exposed infants. Therefore, replication cohorts are necessary to validate this epidemiological finding.

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332 FIGURE LEGENDS

333 Figure 1 | Flow chart of study participants.