Pediatric Surgery International (2019) 35:357–363
https://doi.org/10.1007/s00383-018-4408-0

ORIGINAL ARTICLE

Developmental outcome at 3 years of age of infants following surgery for infantile hypertrophic pyloric stenosis

Alison Loughran-Fowlds[1,2] · Dermot T. McDowell[2,3] · Claire Galea[1,4] · Robert Halliday[1] · Karen Walker[1,2,4] · Nadia Badawi[1,2,4] · Andrew J. A. Holland[2,3]

Accepted: 30 October 2018 / Published online: 7 November 2018

Abstract

Purpose The study compared neurodevelopmental outcome at 3 years of age of infants with infantile hypertrophic pyloric stenosis (IHPS) who underwent pyloromyotomy with healthy control infants in New South Wales, Australia.

Methods Infants with IHPS as well as controls were recruited between August 2006 and July 2008. Developmental assessments were performed using the Bayley scales of infant and toddler development (version III) (BSITD-III) at 1 and 3 years of age.

Results Of the 43 infants originally assessed at 1 year, 39 returned for assessment at 3 years (90%). The majority were term infants (77%). Assessments were also performed on 156 control infants. Infants with IHPS scored significantly lower on four of the five Bayley subsets (cognitive, receptive and expressive language and fine motor) compared to control infants. Analysis of co-variance showed statistically significant results in favour of the control group for these four subsets.

Conclusion Compared with the outcomes at 1 year, infants with IHPS at 3 years of age continue to score below controls in four of the BSITD-III subscales. This suggests they should have developmental follow-up with targeted clinical intervention. There is a need for further studies into functional impact and longer term outcomes.

Keywords Infantile hypertrophic pyloric stenosis · Neonate · Outcome · Development

Abbreviations

IHPS	Infantile hypertrophic pyloric stenosis
BSITD-III	Bayley scales of infant and toddler development (version III)
GA	General anaesthesia

✉ Alison Loughran-Fowlds
alison.loughranfowlds@health.nsw.gov.au

[1] Grace Centre for Newborn Intensive Care, The Children's Hospital at Westmead, Sydney Children's Hospitals Network, Locked Bag 4001, Westmead, NSW 2145, Australia

[2] Sydney Medical School, The University of Sydney, Sydney, Australia

[3] Douglas Cohen Department of Paediatric Surgery, The Children's Hospital at Westmead, Sydney Children's Hospitals Network, Sydney, Australia

[4] The Cerebral Palsy Alliance, Sydney, Australia

Purpose

Infantile hypertrophic pyloric stenosis (IHPS) is one of the commonest surgical conditions in infancy [1]. Musculature hypertrophy of the pylorus results in a gastric outlet obstruction, typically presenting before 3 months of age [2, 3]. Whilst the aetiology of IHPS remains unclear, surgical approaches favoured today include laparoscopic or open pyloromyotomy under general anaesthesia (GA) [1, 3]. Recent evidence demonstrates equivalence between either approach regarding complication rates and operating times [1, 4–7]. Pyloromyotomy has been considered a "relatively simple procedure with an excellent outcome" [2].

Concern has been raised about risks of long-term developmental outcomes following major surgery [8–10], although it is less clear whether comparatively simple surgery, such as pyloromyotomy, may also contribute to long-term neurodevelopmental delay. Neurodevelopmental delay following surgery is likely to be multifactorial in origin including genetic and maternal factors, pre-operative clinical condition, gender and prematurity [9, 11]. Controversy surrounds the degree to which operative factors may contribute including duration of procedure, and the number and type of anaesthetic and analgesic agents utilised [12–14]. It is unclear which of these factors may also be applicable for infants undergoing pyloromytomy.

Although there remains limited literature on specific developmental outcomes following pyloromyotomy, our previous study found that infants who underwent pyloromyotomy under GA had developmental scores that were lower compared to matched healthy control infants at 1 year of age [15]. It is unknown whether this delay persists and what the contributing factors might be.

Infants with IHPS were enrolled in a prospective study and at the 1-year developmental assessment it was noticed that concurrent infants with IHPS scored lower on the assessment, thus the 1-year outcomes were reviewed and published [15]. As the 1-year developmental outcomes of infants who underwent pyloromyotomy for IHPS were lower than healthy normal controls [15], we sought to evaluate the developmental outcomes of these patients at 3 years of age to determine whether neurodevelopmental delay persisted and what factors may contribute to the risk of developmental delay.

Methods

Study design and population

Infants were prospectively enrolled as part of a larger population-based study which aimed to compare the developmental outcomes of infants who had undergone early cardiac and non-cardiac major surgeries within the first 3 months of life with their healthy peer controls in NSW, Australia (DAISy study). Infants who had a surgical correction of IHPS in one of the three children's hospitals in NSW and who had a developmental assessment at 3 years of age were eligible. The operative modality, open or laparoscopic, was based on the treating surgeons' preference. Data were collected on the operative modality, operative time, and intra- and post-operative complications. Infants were excluded if they had associated congenital disorders which affect neurodevelopment, such as Trisomy 21. Control infants were selected randomly from co-located maternity hospitals; these infants were enrolled between August 2006 and July 2008.

Ethical approval was obtained individually from all the participating health services with informed consent obtained directly from parents or carers.

Developmental assessment

At 3 years of age, the children were reassessed using The Bayley Scales of Infant and Toddler Development (version III) (BSITD-III) [16] which is a standardised assessment, validated in the United States of America (USA), using examination of infant skills rather than a parental questionnaire. This assessment is internationally validated and has been used in our earlier studies [9, 15]. The assessment consists of five scales: cognition, receptive language, expressive language, fine motor and gross motor. Developmentally trained clinicians certified and experienced in the assessment tool, one of whom was blinded to the infant's study group, assessed the children against the standardised scoring system for the assessment. The five subscales were reported individually instead of using the composite scores to identify differences between the subsections of the language and the motor scales which would not be evident with composite scores alone.

Data analysis

Normality was checked using Shapiro–Wilk and visual inspection of box plots. Descriptive statistics were used for demographic variables reported as median and IQR as normality assumptions failed. Mean and standard deviation were also reported for clinical interpretation. Between-group differences on demographic variables were conducted using Mann–Whitney *U* test. Each of the mean scores of the five subscales was compared with the standardised norms of the BSID-III assessment. Developmental test results were compared with published norms, and delay was defined as deviating from normative data [16]. This standardised test of infant development is age normed to have a mean of 10 and a standard deviation of 3. The mean differences from the standardised norm of 10 was calculated for each of the scaled scores on the five subscales for each of the three groups and significance determined using one-sample t-tests. Chi-squared associations were examined for comparison of parameters against the Bayley scores. Between-group differences were conducted using independent t-test to assist in clinical reporting using mean and standard deviation. Spearman's rho non-parametric correlation was performed between 1- and 3-year Bayley's. Outliers for the IHPS group were identified by visual inspection of boxplots. Any outliers in the control group remained in the analysis for clinical interpretation. Gain scores were calculated by subtracting the Bayley score at 1 year from the corresponding Bayley score at 3 years for each of the five subdomains. To account for baseline differences, an analysis of co-variance (ANCOVA) was undertaken and reported using estimated mean and 95% CI. Individual trajectories were assessed visually on all five subdomains for the treatment group. Mann–Whitney *U* tests for between-group difference were conducted for infants lost to follow-up. A *p* value of < 0.05 was considered significant. Data were analysed using SPSS for Windows, version 21 (IBM, Armonk, New York, USA).

Results

Of the 43 infants assessed at 1 year of age, 39 children (90%) were able to be reassessed at 3 years of age. There were four children who were lost to follow-up. Two children had additional associated congenital anomalies (anorectal malformation, unilateral hydronephrosis). Developmental outcomes were compared to those of the 155 control infants.

The mean gestation age for the infants with IHPS was 38 weeks, and the median birth weight was 3300 g compared to control infants who had a mean gestation of 39 weeks and mean birth weight 3553 g. Most infants with IHPS were male (29/39, 74%) and three infants were preterm (Table 1). No infants died from either the IHPS group or the control group. The median age at which the infants presented was 30.8 days (10–77 days). The clinical diagnosis of IHPS was confirmed by ultrasound in the majority (83%) of infants and most (86%) had an open pyloromyotomy, with only 14% having a laparoscopic pyloromyotomy. The median length of stay was 4 days (range, 2–13 days).

The only statistically significant difference between males and females who had IHPS when compared to continuous Bayley scores was for cognition ($p=0.006$). There was no association between birth order and Bayley scores.

Analysis was performed on centile of body weight, sodium, potassium and initial pH levels of infants on admission; there were no associations between these parameters and developmental scores, or between genders. Length of vomiting history similarly had no association with Bayley scores except for a weak association with later receptive language scores ($p=0.045$). There was no significant correlation between length of time of the procedure and outcome at 3 years. No infant had an identified major intra- or post-operative complication which could be analysed against later developmental outcomes. Too few children had a laparoscopic approach to be able to analyse operative modality versus outcomes.

Across all five subdomains, the IHPS group had lower scores on the Bayley at 1 year (Table 2). At 3 years, the mean scores for infants with IHPS were all within the average range for each subset (Table 3). Although worryingly, however, these infants had significantly lower scores compared to control infants in four of the five developmental subsets at 3 years: cognition Treatment 9.18 (1.83) versus Control 10.35(1.89) ($p=0.001$), receptive Treatment 10.18 (2.60) versus Control 11.44 (2.11) ($p=0.002$), expressive language Treatment 9.95 (2.40) versus Control 11.01 (2.61) ($p=0.018$), and fine motor subsets Treatment 10.24 (2.05) versus Controls 11.37 (2.07) ($p=0.003$). Gross motor skills were not significantly different between infants with IHPS and control

Table 1 Demographic variables of infants with infantile hypertrophic pyloric stenosis versus control infants at 1 year

	IHPS	Control	*P* value
Gender *n* (%)	Boys: 29 (74%) Girls: 10 (26%)	Boys: 86 (55%) Girls: 70 (45%)	0.029
GA Mean (SD) Median (IQR)	38.43 (2.133) 38.50 (3)	39.46 (1.138) 40.00 (1.00)	0.002
BW Mean (SD) Median (IQR)	3312.18 (619.950) 3405.00 (654)	3553.01 (500.075) 3540.00 (691.25)	0.018

N number, *GA* gestational age, *SD* standard deviation, *BW* birth weight, *IQR* interquartile range, *IHPS* infantile hypertrophic pyloric stenosis

Table 2 Developmental outcomes of infants with infantile hypertrophic pyloric stenosis versus control infants at 1 year

	Bayley at 1-year scaled scores		Gain score mean and standard deviation	
	IHPS $n=39$ Mean (SD) Range	Control $n=156$ Mean (SD) Range	IHPS $n=37$ MD (SD)	Control $n=156$ MD (SD)
Cognition	10.85 (2.30) 10	11.72 (2.27) 13	− 1.67 (2.59)	− 1.37 (2.75)
Receptive language	9.74 (2.48) 11	11.22 (2.43) 14	0.47 (2.87)	0.22 (2.76)
Expressive language	9.05 (2.82) 13	9.96 (1.80) 10	0.90 (2.55)	1.06 (2.94)
Fine motor	8.85 (2.82) 10	9.99 (2.13) 8	1.43 (2.35)	1.38 (2.53)
Gross motor	8.10 (3.09) 13	9.49 (2.67) 18	1.46 (3.97)	0.40 (2.85)

Mean, standard deviation (SD) and range for raw scores, gain score mean difference (MD) and SD

IHPS infantile hypertrophic pyloric stenosis

Table 3 Developmental outcomes of infants with infantile hypertrophic pyloric stenosis versus control infants at 3 years

	IHPS $n=39$ Mean	Control $n=156$ Mean	*P* value	95% CI	
Cognition	9.18	10.37	0.001	0.519	1.858
Receptive language	10.18	11.44	0.002	0.452	2.057
Expressive language	9.95	11.05	0.018	0.187	2.005
Fine motor	10.24	11.39	0.003	0.394	1.893
Gross motor	9.57	9.89	0.389	− 0.414	1.060

IHPS infantile hypertrophic pyloric stenosis, *N* number, *95% CI* 95% confidence intervals

infants Treatment 9.57 (2.72) versus Controls 9.88 (1.84) ($p=0.505$). The Spearman's rho non-parametric correlation between 1 and 3 years across the five subdomains varied but was all <0.509. This would suggest there was a real effect and not part of the natural variation.

Gain scores showed the IHPS group to have higher mean differences for all categories except expressive language (Table 2). ANCOVA analysis was conducted with outliers removed ($n=2$ from the IHPS group) and demonstrated a statistically significant difference between groups when accounting for baseline on all subdomains ($p<0.05$) (Table 4). These results were in favour of the control group in all subdomains except gross motor.

Individual trajectories for the IHPS group with outliers included demonstrated clearly the wide range of baseline values. These trajectories showed low gross motor baseline values for the IHPS group compared to the other four subdomains, although the trend does improve. Mann–Whitney U tests for between-group difference were conducted for infants lost to follow-up and all *p* values were greater than >0.322; therefore, there was no difference in scores and hence no attrition bias.

Discussion

Our study is the first to our knowledge to examine longitudinal neurodevelopmental outcomes of IHPS. It is concerning that statistically significant neurodevelopmental delay appears to persist from 1 until 3 years of age and can stem from a relatively 'minor' surgical conditions such as IHPS [2, 15]. This finding of lower than expected developmental scores in IHPS infants compared to a large cohort of normal control infants raises a question about the potential impact of IHPS and its surgical treatment.

Although infants with IHPS had mean developmental scores within the average range at 3 years, they were still significantly lower than control infants in four of the five subsections of the BSITD-III. This means a significantly higher number of infants with IHPS will have developmental scores below the average range compared to controls. Disturbingly, the BSITD-III assessment, although an international gold standard for assessment of neurodevelopment, routinely underestimates severity of delay in the Australian population [17, 18] and, therefore, may miss more subtle neurodevelopmental issues. Thus, the scores in IHPS infants may actually be of greater concern than is reflected in the BSIDTD-III. It is difficult, however, to know how much these results mean in real life and over the longer term later into childhood, as there is a lack of longer term standardised developmental follow-up into school age available for these children in Australia.

These findings were similar to the results at 1 year of age where infants with IHPS scored lower than controls in four areas—cognitive, receptive language, fine motor and gross motor [15]. Expressive language scores became of concern at age three; the BSITD-III assessment of expressive language is more complex at 3 years and thus may pick up more subtle concerns than at age one. Gross motor scores were no longer impaired at age three, which may be due to natural progression with catch-up of skills.

Table 4 ANCOVA analysis for infants with infantile hypertrophic pyloric stenosis versus control infants

	ANCOVA			
	IHPS $n=37$ Mean (95% CI)	Control $n=156$ Mean (95% CI)	Mean difference (95% CI)	*p* value
Cognition	9.54 (8.96–10.11)	10.33 (10.05–10.61)	− 0.792 (− 1.44 to − 0.15)	0.016
Receptive language	10.91 (10.24–11.59)	11.37 (11.05–11.69)	− 0.457 (− 1.21 to 0.29)	0.008
Expressive language	10.44 (9.65–11.24)	10.99 (10.60–11.37)	− 0.541 (− 1.43 to 0.34)	0.008
Fine motor	10.84 (10.20–11.49)	11.32 (11.02–11.62)	− 0.476 (− 1.19 to 0.24)	0.009
Gross motor	10.10 (9.46–10.74)	9.85 (9.55–10.15)	0.245 (− 0.47 to 0.96)	0.002

IHPS infantile hypertrophic pyloric stenosis, *MD* mean difference, *SD* standard deviation, *95% CI* 95% Confidence interval

The reasons why these differences are seen in IHPS infants are unclear but are likely to be multifactorial. It is difficult to know whether the findings are related to IHPS specifically, secondary to anaesthesia or environmental factors related to hospital stay. They may be related to the IHPS through a common genetic aetiology [19]. The role of anaesthesia remains controversial; exposure to anaesthesia in early childhood has been associated with apoptosis in primates [20] and with later learning disability in children even in relatively minor procedures [12, 21], although other studies have shown no evidence of harm from short anaesthetics [13, 14, 22]. The US Food and Drug Administration currently warns that "repeated or lengthy use of general anaesthesia and sedation drugs in children younger than 3 years of age may affect the development of children's brains", although their advice also includes in the statement that surgery for IHPS should not be delayed [23]. The relationship between neuromuscular blocking agents and post-operative prolonged skeletal muscle weakness is controversial although recent prospective studies suggest that these agents may be less at fault than first thought and bolus/short-term administration should be considered safe [24]. Some studies have found that single, short-duration anaesthetics do not affect later neurodevelopment to a significant extent [13, 21, 25]. A statement on the relationship of anaesthetics and neurodevelopment on our website is available and has been referenced by the Therapeutic Goods Administration, Department of Health [26]. In our study, operative time did not show a difference in outcomes; however numbers were too small to analyse operative modality. No infants in our study had major complications. Studies of larger number of infants are needed to examine more closely the effects of operative time, operative modality including longer time required for laparoscopic operations, anaesthetic drugs, complications and anaesthesia drugs on developmental outcomes in this population.

Nutrition and impaired electrolytes may play a role through their effect on early brain development [27]; although as the time to diagnosis is usually relatively short, these factors are unlikely to be of major significance, as shown by our results [28]. The weak association of vomiting to receptive language scores should be interpreted with caution due to the small number of infants involved and the spread of number of vomiting days.

ANCOVA analysis was undertaken to control for the differences in baseline score at 1 year. This analysis clearly demonstrated between-group differences for all subscales except gross motor. This was surprising; there may be a difference in gross motor in reality; however, the statistical approach may not be sufficiently sensitive to demonstrate a difference if one exists.

For the paediatric surgeon, the optimal approach would seem to be to optimise the infants' physiological status prior to pyloromyotomy, through appropriate rehydration, correction of any electrolyte imbalances and, if necessary, following a period of nutritional supplementation. Surgery should be performed expeditiously under general anaesthesia by appropriate trained and credentialed clinicians to minimise the duration of surgery and anaesthesia. Alternatives to general anaesthesia, such as awake surgery and spinal anaesthesia, should be explored with research comparing outcomes with operations under general anaesthesia. Finally, and perhaps most importantly, these infants should have their developmental status reviewed following surgery so that as they continue to grow any delays can be expeditiously identified intervention arranged.

Limitations of this study include the small number of infants. Although weight was measured on admission, accurate weight loss data were not obtained and so were unable to be analysed, which would be a better measure of the impact of the disorder. A major limitation is that these IHPS infants were compared against control infants who were not admitted to hospital. Ideally to tease out whether hospital stay is a factor versus IHPS or anaesthetic development could be compared to infants admitted to hospital for other non-surgical reasons; however, these infants are not routinely followed up in our developmental follow-up clinics and thus scores are unavailable for comparison. A further limitation is the inability to compare open versus laparoscopic procedures due to the small numbers of laparoscopic procedures. Parental factors were also not collected at the time of admission. Therefore, factors that also affect development such as ethnicity, parental education and age, income and social factors were not available for analysis. Also as these children were assessed for research and not in clinical follow-up assessment programmes, and as follow-up is not available past the age of 3 years in our institution, there are no data available on what the Bayley scores functionally meant for these children, especially into school age. Despite this, it is reassuring that infants with IHPS still had scores within the average range at 3 years of age.

These infants have an increased risk of developmental delay at 3 years; however, it is difficult to know whether these infants will have longer term problems with their development and/or function. These infants should be followed up routinely after surgery to make sure their neurodevelopmental gains are optimised [15]. Multidisciplinary follow-up of all infants with IHPS in a specialised clinic is impractical. However, all infants admitted to neonatal intensive care units and who have early surgery should have standardised developmental assessment as per international recommendations. Follow-up of IHPS infants not admitted to a neonatal intensive care unit should at least include regular developmental assessments with their general practitioners and health clinics. Assessing children 3 years of age provides the opportunity for parents to identify issues prior to school entry, allowing time for early identification of specific problems, especially with reading and other cognitive skills. Any child who has a lower score on a developmental assessment is at risk and should be referred for assessment to the appropriate therapist. Longer term follow-up of these infants past 3 years of age is recommended to assess whether differences in development persist and what this functionally means for children into school age. Adequate data collection is also essential to tease out underlying reasons for positive findings.

Conclusions

Compared with the outcomes at 1 year, infants with IHPS continue to score below the controls in four of the BSITD-III subscales, although overall the means remain within the average range. These data remain concerning and the findings raise the need for further studies including continuing development review to determine whether these differences persist into later childhood, and their functional importance. It may be appropriate to screen patients with IHPS at follow-up and consider targeted clinical intervention to remediate any neurodevelopmental issues identified to ensure an optimal long-term outcome in these infants. Surgery should be performed expeditiously under general anaesthesia by appropriate trained and credentialed clinicians to minimise the duration of surgery and anaesthesia.

Acknowledgements We thank the parents and carers, and also surgical colleagues who gave permission for their infants to be enrolled in this study.

Funding The DAISy study was initially funded by the March of Dimes Birth Defects Foundation (Grant 12-FY06-232). No funding grants were obtained or required for this study.

Compliance with ethical standards

Conflict of interest Alison Loughran-Fowlds declares she has no conflict of interest. Dermot T. McDowell declares he has no conflict of interest. Claire Galeaa declares she has no conflict of interest. Robert Halliday declares he has no conflict of interest. Karen Walker declares she has no conflict of interest. Nadia Badawi declares she has no conflict of interest. Andrew J. A. Holland declares he has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

References

1. St Peter SD, Ostlie DJ (2008) Pyloric stenosis: from a retrospective analysis to a prospective clinical trial—the impact on surgical outcomes. Curr Opin Pediatr 20:311–314. https://doi.org/10.1097/MOP.0b013e3282ff0de9
2. Aspelund G, Langer JC (2007) Current management of hypertrophic pyloric stenosis. Semin Pediatr Surg 16:27–33. https://doi.org/10.1053/j.sempedsurg.2006.10.004
3. Chung E (2008) Infantile hypertrophic pyloric stenosis: genes and environment. Arch Dis Child 93:1003–1004. https://doi.org/10.1136/adc.2008.141499
4. Adibe OO, Nichol PF, Flake AW, Mattei P (2006) Comparison of outcomes after laparoscopic and open pyloromyotomy at a high-volume pediatric teaching hospital. J Pediatr Surg 41:1676–1678. https://doi.org/10.1016/j.jpedsurg.2006.05.051
5. Oomen MW, Hoekstra LT, Bakx R, Ubbink DT, Heij HA (2012) Open versus laparoscopic pyloromyotomy for hypertrophic pyloric stenosis: a systematic review and meta-analysis focusing on major complications. Surg Endosc 26:2104–2110. https://doi.org/10.1007/s00464-012-2174-y
6. Safford SD, Pietrobon R, Safford KM, Martins H, Skinner MA, Rice HE (2005) A study of 11,003 patients with hypertrophic pyloric stenosis and the association between surgeon and hospital volume and outcomes. J Pediatr Surg 40:967–972. https://doi.org/10.1016/j.jpedsurg.2005.03.011
7. Yagmurlu A, Barnhart DC, Vernon A, Georgeson KE, Harmon CM (2004) Comparison of the incidence of complications in open and laparoscopic pyloromyotomy: a concurrent single institution series. J Pediatr Surg 39:292–296. PMID: 15017540
8. Gischler SJ, Mazer P, Duivenvoorden HJ, van Dijk M, Bax NMA, Hazebroek FWJ, Tibboel D (2009) Interdisciplinary structural follow-up of surgical newborns: a prospective evaluation. J Pediatr Surg 44:1382–1389. https://doi.org/10.1016/j.jpedsurg.2008.12.034
9. Walker K, Loughran-Fowlds A, Halliday R, Holland AJ, Stewart J, Sholler GF, Winlaw DS, Badawi N (2015) Developmental outcomes at 3 years of age following major non-cardiac and cardiac surgery in term infants: a population-based study. J Paediatr Child Health 51:1221–1225. https://doi.org/10.1111/jpc.12943
10. Filan PM, Hunt RW, Anderson PJ, Doyle LW, Inder TE (2012) Neurologic outcomes in very preterm infants undergoing surgery. J Pediatr 160:409–414. https://doi.org/10.1016/j.jpeds.2011.09.009
11. Glatz P, Sandin RH, Pedersen NL, Bonamy AK, Eriksson LI, Granath F (2017) Association of anesthesia and surgery during childhood with long-term academic performance. JAMA Pediatr 171:e163470. https://doi.org/10.1001/jamapediatrics.2016.3470
12. DiMaggio C, Sun LS, Kakavouli A, Byrne MW, Li G (2009) A retrospective cohort study of the association of anesthesia and hernia repair surgery with behavioral and developmental disorders in young children. J Neurosurg Anesthesiol 21:286–291. https://doi.org/10.1097/ANA.0b013e3181a71f11
13. Bartels M, Althoff RR, Boomsma DI (2009) Anesthesia and cognitive performance in children: no evidence for a causal relationship. Twin Res Hum Genet 12:246–253. https://doi.org/10.1375/twin.12.3.246
14. Davidson AJ, Disma N, de Graaff JC, Withington DE, Dorris L, Bell G et al (2016) Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial. Lancet 387:239–250. https://doi.org/10.1016/S0140-6736(15)00608-X
15. Walker K, Halliday R, Holland AJ, Karskens C, Badawi N (2010) Early developmental outcome of infants with infantile

hypertrophic pyloric stenosis. J Pediatr Surg 45:2369–2372. https://doi.org/10.1016/j.jpedsurg.2010.08.035

16. Bayley N (2006) Bayley scales of infant and toddler development, 3rd edn. The Psychological Corporation, San Antonio
17. Chinta S, Walker K, Halliday R, Loughran-Fowlds A, Badawi N (2014) A comparison of the performance of healthy Australian 3-year-olds with the standardised norms of the Bayley scales of infant and toddler development (version-III). Arch Dis Child 99:621–624. https://doi.org/10.1136/archdischild-2013-304834
18. Anderson PJ, De Luca CR, Hutchinson E, Roberts G, Doyle LW, Victorian Infant Collaborative Group (2010) Underestimation of developmental delay by the new Bayley-III Scale. Arch Pediatr Adolesc Med 164:352–356. https://doi.org/10.1001/archpediatrics.2010.20
19. Krogh C, Fischer TK, Skotte L, Biggar RJ, Oyen N, Skytthe A, Goertz S, Christensen K, Wohlfahrt J, Melbye M (2010) Familial aggregation and heritability of pyloric stenosis. JAMA 303:2393–2399. https://doi.org/10.1001/jama.2010.784
20. Brambrink AM, Evers AS, Avidan MS, Farber NB, Smith DJ, Zhang X, Dissen GA, Creeley CE, Olney JW (2010) Isoflurane-induced neuroapoptosis in the neonatal rhesus macaque brain. Anesthesiology 112:834–841. https://doi.org/10.1097/ALN.0b013e3181d049cd
21. Wilder RT, Flick RP, Sprung J, Katusic SK, Barbaresi WJ, Mickelson C, Gleich SJ, Schroeder DR, Weaver AL, Warner DO (2009) Early exposure to anesthesia and learning disabilities in a population-based birth cohort. Anesthesiology 110:796–804. https://doi.org/10.1097/01.anes.0000344728.34332.5d
22. Sun LS, Li G, Miller TL, Salorio C, Byrne MW, Bellinger DC et al (2016) Association between a single general anesthesia exposure before age 36 months and neurocognitive outcomes in later childhood. JAMA 315:2312–2320. https://doi.org/10.1001/jama.2016.6967
23. The US Food and Drug Administration (2017) FDA review results in new warnings about using general anesthetics and sedation drugs in young children and pregnant women. https://www.fda.gov/downloads/Drugs/DrugSafety/UCM533197.pdf. Accessed 19 Sep 2017
24. deBacker J, Hart N, Fan E (2016) Neuromuscular blockade in the 21st century management of the critically ill patient. Chest 151:697–706. https://doi.org/10.1016/j.chest.2016.10.040
25. Flick RP, Katusic SK, Colligan RC, Wilder RT, Voigt RG, Olson MD, Sprung J, Weaver AL, Schroeder DR, Warner DO (2011) Cognitive and behavioral outcomes after early exposure to anesthesia and surgery. Pediatrics 128:e1053–e1061. https://doi.org/10.1542/peds.2011-0351
26. deLima J (2017) Departmental statement regarding potential neurotoxicity of anaesthetic agents in children. The Sydney Children's Hospitals Network. https://www.schn.health.nsw.gov.au/files/attachments/anaesthesia_related_neurotoxicityv2.pdf. Accessed 29 Oct 2018
27. Keunen K, van Elburg RM, van Bel F, Benders MJ (2015) Impact of nutrition on brain development and its neuroprotective implications following preterm birth. Pediatr Res 77:148–155. https://doi.org/10.1038/pr.2014.171
28. Taylor ND, Cass DT, Holland AJ (2013) Infantile hypertrophic pyloric stenosis: has anything changed? J Paediatr Child Health 49:33–37. https://doi.org/10.1111/jpc.12027