Necrotizing Enterocolitis in Neonates: Has the Brain Taken a Hit 10 Years Later?

Ankita Mondal, Devesh Misra1,2, Ahmed Al-Jabir, Dalal Hubail, Thomas Ward, Bijendra Patel1

Introduction

Pediatric surgery literature on necrotizing enterocolitis (NEC) tends to concentrate on gastrointestinal morbidity such as short gut syndrome, often neglecting neurological status.[1,2] Long-term neurological impairment has been noted in preterm and low birth weight infants, per se. Severe systemic inflammation, as seen in NEC, can additionally compound this problem by impairing oligodendrocyte development.[3] NEC is often fatal, limiting the feasibility of large-scale, long-term neurodevelopmental assessment studies. Validated neurodevelopment assessment tools also tend to focus on infant and toddler development with a seminal check at 2 years, further resulting in generally shorter-term follow-up of neurodevelopment in survivors. This paper thus seeks to follow-up patients diagnosed with NEC as neonates, 10 years down the line.

Background: The neonate with necrotizing enterocolitis (NEC) is at risk of developing poor neurodevelopmental outcomes. There is a dearth of long-term follow-up studies in this field, with a majority of studies reporting a follow-up duration of 2 years. The aim of this study was to assess neurodevelopment of babies diagnosed with NEC more than a decade ago. This study was carried out in a tertiary hospital with neonatal surgery and intensive care units. Materials and Methods: Retrospective review of notes and telephone interviews with parents of babies diagnosed with NEC between January 2007 and December 2008 was conducted. Evidence of motor, cognitive, and sensory impairment was recorded. Fisher’s exact, χ², and unpaired t-tests were used. P-values <0.05 were considered significant. Results: Overall mortality in this cohort was 31%. Eighteen patients were followed up to an average age of 11.2 years. Of the 18 patients, 11 (61%) had a neurological impairment. Of the 15 surgically managed patients, 10 (67%) had an impairment and, of the 3 medically managed patients, 1 (33%) had an impairment. Cognitive impairment was the most common (10/18, 56%), followed by motor (6/18, 33%). Ten of 18 (56%) had special education needs, 9 of 18 (50%) had learning difficulties, 6 of 18 (33%) had speaking difficulties, and 4 of 18 (22%) had cerebral palsy. Patients also had behavioral conditions (3/18, 17%), visual impairment (2/18, 11%), and seizures (2/18, 11%). Conclusion: In the field of NEC, there is a hidden neurological burden that neonatal surgeons bequeath to the community. Sixty-one percent of patients are neurologically impaired, affecting the quality of life and function in the long-term. There should be appropriate parent counseling at the point of diagnosis and regular development checks for children with NEC.

Keywords: Long-term follow-up, necrotizing enterocolitis, neurodevelopment
A review of the current literature on neurodevelopment in NEC was also carried out.

**Materials and Methods**

NICU register was searched for patients diagnosed with NEC between January 2006 and December 2007. A retrospective review of case notes and electronic patient records (EPR) was carried out. The presence of the following conditions, used in previous studies to illustrate “neurodevelopment impairment,” was noted where applicable:

- Epilepsy, blindness, deafness, speaking difficulties, cerebral palsy (CP), special education needs (SEN), learning disabilities (LD), behavioral issues such as autism spectrum disorder and attention deficit and hyperactivity disorder, and dyspraxia.

Telephone interviews with parents were conducted to confirm EPR findings for alive patients. A template for the telephone interview can be seen as in Figure 1. Impairment was classified as cognitive (SEN, LD, and behavioral issues), motor (CP, dyspraxia, and speaking difficulties), sensory (blindness and hearing loss), or others (epilepsy).

The following search was conducted on PubMed for literature review: (((outcome) OR impairment) OR cognitive) OR neurodevelopment) AND (((NEC) OR necrotizing enterocolitis) OR necrotizing enterocolitis). Original research articles written in English were included, with no restrictions placed on the date of publication. Only studies which controlled for factors such as prematurity and low birth weight were included.

**Ethics approval**

The case series was registered as a clinical governance project. All information was confidential and anonymized.

---

1. Could I please confirm your child’s full name and date of birth?
2. Could you please confirm that ___ was born at x weeks, and weighed y at birth?
3. Could you please confirm that soon after birth, ___ was diagnosed with Necrotising Enterocolitis?
4. Did ___ require surgery for Necrotising Enterocolitis?
5. Does ___ have any current seizures?
6. Does ___ have any current seizures?
7. Does ___ require glasses to see? Are they registered visually impaired?
8. Is ___ able to move like other children their age? Is there a diagnosis of Cerebral Palsy? Could you please tell me more?
9. Does ___ experience difficulty in speaking?
10. Currently, does ___ attend school? Are there any special arrangements made at school? Could you explain more about the arrangements made?
11. Does ___ attend “special school”?
12. Has ___ been diagnosed with any learning difficulties? Are these learning difficulties general, or have you been told that ___ has dyslexia, dyscalculia or dyspraxia?
13. Does ___ have any diagnosis of Autism or ADHD?
14. Are there any other behavioural problems that ___ has?
15. Was ___ able to give their Key Stage 1 examinations? How did they go; were they placed below average of the cohort at all?
16. Do you have any questions for me?

Blanks indicate patient’s name

**Figure 1: Template used for follow-up telephone questionnaire**

---

**Statistics**

Fisher’s exact tests, χ² tests, and unpaired t-tests were used to compare groups. SPSS (Version 25; IBM Corp., Armonk, NY, USA) was used for analyses. All P-values <0.05 were considered statistically significant.

**Results**

In total, 67 patients were diagnosed with NEC from January 2006 to December 2007. The mean birth weight was 1216 g (470–3580 g). The mean gestational age was 29 weeks (23–41 weeks). There was 31% overall mortality (21/67). The mean age at the time of death was 40 days (1–209 days).

Of 46 alive patients, 18 (39%) were contacted. The mean age of the patients followed up was 11.2 (10.5–12.3) years. There were no significant differences in gestational age and birth weight for the group which was followed up and the group which was lost to follow-up (P = 0.9, 0.65, respectively). Prevalence of surgical management between the two groups was also not significantly different (P = 1).

Of 18 patients contacted, 11 (61%) had some form of neurological impairment. Sex, ethnicity, incidence of multiple births, gestational age, and birth weight of the babies were not seen to be statistically different between those who had a neurological impairment and those who did not (P = 0.3, 0.1, 1, 0.8, and 0.9, respectively).

The most common form of neurological impairment was cognitive impairment [Table 1]. Note that some forms of impairment result in a total higher than the total number of children with impairment, as some children had multiple forms of impairment.

Ten of 15 (67%) patients with NEC requiring surgical management (sNEC) and one of three (33%) patients with NEC requiring only medical management (mNEC) had neurological impairment. Though not statistically significant (P = 0.528), patients with sNEC within our cohort were 3.143 times more likely to be neurologically impaired than their mNEC counterparts (RR = 3.143, 95% CI 0.346–26.520).

**Literature review**

Literature review yielded 25 articles which met the inclusion/exclusion criteria. Thirteen were cohort studies and 12 were case-control studies. Nineteen (78%) had a maximum follow-up duration of 24 ± 2 months. The median number of patients in a study was 20, and the mode was 12.

There was a lack of consensus in literature review regarding independent effects of NEC on neurodevelopment. While more studies found
significantly higher rates of neurological impairment in children with NEC, some papers found the differences to be insignificant.\cite{17,21} All papers which compared babies with sNEC to those with no NEC, however, found significantly higher levels of impairment.\cite{22-27} Conversely, when analyzing studies which compared babies with mNEC with babies who did not develop NEC, we found that more studies found that differences in neurodevelopment between the two cohorts were not statistically significant.\cite{15,22,23,26,27}

**DISCUSSION**

Neurodevelopment refers to the development and maturation of the central nervous system. At its basic, it involves the delicate balance of processes such as neuron generation and growth, synaptogenesis, and neurohormone production.\cite{28-30} Starting *in utero*, neurodevelopment continues well into adult life, as reflected by the Diagnostic and Statistical Manual of Mental Disorders Edition 5 (DSM-5) definition of “neurodevelopment disorders” being deficits in “personal, social, academic, or occupational functioning.”\cite{31}

Premature neonates undergo a seminal check at 24 months age. Correspondingly, most validated forms of neurodevelopment assessment have a major checkpoint at this age. Therefore, most studies on neurodevelopment outcomes in NEC have reported a mean follow-up of 2 years. Our study, however, has a mean follow-up of 11.2 years. As mentioned, neurodevelopment continues beyond infancy, and this much longer follow-up duration allows for a better understanding of the long-term effects of NEC on neurodevelopment.

The majority (61%) of our children diagnosed with NEC as neonates had neurodevelopment impairment persisting into late childhood. This is a high percentage, and while this study does not directly compare with similar children who did not develop NEC, the suggested pathophysiology of NEC—an inflammatory condition with large cytokine surges—can go toward explaining the large percentage of children with neurological impairment. The cytokine storm seen in inflammatory conditions like NEC may add insult to the oftentimes premature brain, causing damage and resultant neurological impairment.

When looking closer at the subgroup analysis, our study showed that 67% of patients with sNEC had neurological impairment, which is comparable to values ranging from 55% to 57% in literature.\cite{24,25} This was higher than the prevalence in babies with mNEC (33%). While not statistically significant due to the small sample size, this suggests that patients with sNEC are at higher risk than their mNEC counterparts. This is not surprising because neonates needing surgery are sicker with severe metabolic acidosis, presence of shock, and respiratory embarrassment needing ventilation being the norm.\cite{4,16,10} There is also a higher incidence of intraventricular bleeds in surgical patients.\cite{21,23}

Referring back to our literature review, it was noticed that all studies comparing impairment in babies with sNEC with babies who had no NEC found statistically significant differences in impairment between the two groups. In contrast, studies comparing babies with mNEC vs no NEC, mostly found differences in impairment to be insignificant. This suggests that sNEC perhaps has a clearer impact on worsening neurodevelopment. Various hypotheses have been put forward to try and explain this observation. For instance, intraoperative hypothermia and cerebral hypotension have been suggested as possible reasons for the observed worse neurological outcomes in babies undergoing surgery.\cite{32} Surgery is indicated in those with more extensive disease, as judged by using “scoring” systems such as the Bell’s criteria, where a combination of escalating radiological and clinical signs are used to determine whether a baby will require surgical intervention. Surgical intervention for NEC has been shown to also result in higher levels of inflammation and risk of sepsis—further exacerbating cerebral insult. Indeed, it is likely that it is the amalgamation of these factors which result in long-term neurodevelopmental consequences.

There has been, in recent years, interest in the possible role of anesthesia in damaging the brains of neonates undergoing even elective surgery.\cite{33} Neurotoxicity due to repeated exposure to anesthetic agents has been

| Motor impairment (n =15) | Cognitive impairment (n =22) | Sensory impairment (n =3) | Others (n =2) |
|-------------------------|-----------------------------|--------------------------|--------------|
| Speaking difficulties (n =6) | Special Education Needs (n =10) | Blindness (n =2) | Current seizures (n =2) |
| Cerebral Palsy (n =4) | Learning difficulties (n =9) | Hearing impairment (n =1) |
| * Quadruplegia (n =2), hemiplegia (n =1), diplegia (n =1) | Behavioural conditions (n =3) | | |

Table 1: Neurological impairment at follow-up
suggested and research is underway to identify which of the anesthetic agents are kinder to the developing brain.\textsuperscript{[33]}

On follow-up, cognitive impairment was the most common form of impairment. Previous studies have also found this to be the pattern,\textsuperscript{[5]} but a few report motor impairment to be more prevalent.\textsuperscript{[35]} Interestingly, a study by Simon \textit{et al.}\textsuperscript{[36]} describes that differences in motor development between children with sNEC and children with no NEC become less significant with increasing age. A further study by Waugh \textit{et al.}\textsuperscript{[21]} describes how minor signs of CP seemed to “disappear” in their older patients. The higher rates of cognitive rather than motor impairment in our series could thus perhaps be explained by the long follow-up duration.

With the increase in survival of small, preterm babies, it becomes ever more important to have adequate follow-up and recognize that even after these children have made it past their neonatal hurdles, morbidity can extend long into their lives, affecting both themselves as well as the family unit. Studies like this help in decision-making, for it is not only the volatile short term that needs to be considered for these babies.

\textbf{Limitations}

The number of patients followed up was small, as is often the case with rare, fatal conditions such as NEC (the median number of participants in literature was 20). A large number of patients were lost to follow-up (61\%). A myriad of social reasons—babies moving into foster care, families moving away—complicates efforts to follow patients up. While there were no statistically significant differences between the contacted and lost to follow-up groups, there remains the possibility of follow-up bias.

\textbf{Conclusion}

Given that studies have suggested the resolution of some forms of impairment with age, our length of follow-up (11.2 years mean, with the shortest follow-up duration of 10.5 years) is especially useful. 61\% of our patients had some form of neurodevelopment impairment—56\% had SEN requirements, 22\% had CP and 11\% were blind, amongst others.

This is the hidden burden that neonatal surgeons bequeath to the community. Economic studies estimate that the American healthcare system spends $1 billion annually on the neurological care of patients with NEC.\textsuperscript{[2]}

We now mention this study to the parents when we go through the consent process for surgery or later when prognosis is discussed weekly during the usual stormy postoperative period. We also keep this information in perspective when we contemplate the end of life scenario in selected cases.

\textbf{Financial support and sponsorship}

Nil.

\textbf{Conflicts of interest}

There are no conflicts of interest.

\textbf{References}

1. Abdullah F, Zhang Y, Camp M, Mukherjee D, Gabre-Kidan A, Colombani PM, \textit{et al.} Necrotizing enterocolitis in 20,822 infants: analysis of medical and surgical treatments. Available from: http://dxdoiorg/ezproxylibraryqmulacuk/101177/0009922809349161. 2010. [Last accessed on 2018 May 19].

2. Neu J, Walker WA. Necrotizing enterocolitis. Available from: http://dxdoiorg/ezproxylibraryqmulacuk/101056/NEJMra1005408. 2011. [Last accessed on 2018 May 27].

3. Adams-Chapman I, Stoll BJ. Neonatal infection and long-term neurodevelopmental outcome in the preterm infant. Curr Opin Infect Dis 2006;19:290-7.

4. Eicher C, Seitz G, Bevot A, Moll M, Goelz R, Arand J, \textit{et al.} Surgical management of extremely low birth weight infants with neonatal bowel perforation: A single-center experience and a review of the literature. Neonatology 2012;101:285-92.

5. Johnson S, Wolke D, Hennessy E, Marlow N. Educational outcomes in extremely preterm children: Neuropsychological correlates and predictors of attainment. Dev Neuropsychol 2011;36:74-95.

6. Hack M, Taylor HG, Klein N, Eiben R, Schatschneider C, Mercuri-Minich N. School-age outcomes in children with birth weights under 750 g. N Engl J Med 1994;331:753-9.

7. Hack M, Taylor HG, Drotar D, Schluchter M, Cartar L, Andreas L, \textit{et al.} Chronic conditions, functional limitations, and special health care needs of school-aged children born with extremely low-birth-weight in the 1990s. JAMA 2005;294:318-25.

8. Aziz K, Vickar DB, Sauve RS, Etches PC, Pain KS, Robertson CM. Province-based study of neurologic disability of children weighing 500 through 1249 grams at birth in relation to neonatal cerebral ultrasound findings. Pediatrics 1995;95:837-44.

9. Adams-Chapman I, Bann CM, Das A, Goldberg RN, Stoll BJ, Walsh MC, \textit{et al.}; Eunice Kennedy Shriver National Institutes of Child Health and Human Development Neonatal Research Network. Neurodevelopmental outcome in the preterm infant. Curr Opin Crit Care Med 2012;13:183-7.

10. Lodha A, Asztalos E, Moore AM. Cytokine levels in neonatal necrotizing enterocolitis and long-term growth and neurodevelopment. Acta Paediatr 2010;99:338-43.

11. Procianoy RS, Silveira RC. Association between high cytokine levels with white matter injury in preterm infants with sepsis. Pediatr Crit Care Med 2012;13:183-7.

12. Pappas A, Adams-Chapman I, Shankaran S, McDonald SA, Stoll BJ, Laptook AR, \textit{et al.;} Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Neurodevelopmental and behavioral outcomes in extremely premature neonates with ventriculomegaly in the absence of periventricular-intraventricular hemorrhage. JAMA Pediatr 2018;172:32-42.
13. Ping LL, Jiang ZD. Comparison of brainstem auditory evoked response at different click rates between preterm babies after neonatal necrotizing enterocolitis and healthy preterm babies. Neonatology 2014;106:317-22.

14. Saldi M, Sarici SU, Bakar EE, Ozcan O. Neurodevelopmental status of preterm newborns at infancy, born at a tertiary care center in turkey. Am J Perinatol 2010;27:121-8.

15. Shah TA, Meinen-Derr J, Gratton T, Steichen J, Donovan EF, Yolton K, et al. Hospital and neurodevelopmental outcomes of extremely low-birth-weight infants with necrotizing enterocolitis and spontaneous intestinal perforation. J Perinatol 2012;32:552-8.

16. Soraisham AS, Amin HJ, Al-Hindi MY, Singhal N, Sauve RS. Does necrotising enterocolitis impact the neurodevelopmental and growth outcomes in preterm infants with birthweight < or =1250 g? J Paediatr Child Health 2006;42:499-504.

17. Dilli D, Eras Z, Özkan Ulu H, Dilmen U, Durgut Şakrucu E. Does necrotizing enterocolitis affect growth and neurodevelopmental outcome in very low birth weight infants? Pediatr Surg Int 2012;28:471-6.

18. Mayr J, Fasching G, Höllwarth ME. Psychosocial and psychomotoric development of very low birthweight infants with necrotizing enterocolitis. Acta Paediatr Suppl 1994;396:96-100.

19. Rose J, Vassar R, Cahill-Rowley K, Hintz SR, Stevenson DK. Neonatal biomarkers of inflammation: correlates of early neurodevelopment and gait in very-low-birth-weight preterm children. Am J Perinatol 2016;33:71-8.

20. Walsh MC, Kliegman RM, Hack M. Severity of necrotizing enterocolitis: influence on outcome at 2 years of age. Pediatrics 1989;84:808-14.

21. Waugh J, O’Callaghan MJ, Tudhope DI, Mohay HA, Burns YR, Gray PH, et al. Prevalence and aetiology of neurological impairment in extremely low birthweight infants. J Paediatr Child Health 1996;32:120-4.

22. Fullerton BS, Hong CR, Velazco CS, Mercier CE, Morrow KA, Edwards EM, et al. Severe neurodevelopmental disability and healthcare needs among survivors of medical and surgical necrotizing enterocolitis: A prospective cohort study. J Pediatr Surg 2017;53:101-7.

23. Hintz SR, Kendrick DE, Stoll BJ, Vohr BR, Fanaroff AA, Donovan EF, et al.; NICHD Neonatal Research Network. Neurodevelopmental and growth outcomes of extremely low birth weight infants after necrotizing enterocolitis. Pediatrics 2005;115:696-703.

24. Tobiansky R, Liu K, Roberts S, Veddovi M. Neurodevelopmental outcome in very low birthweight infants with necrotizing enterocolitis requiring surgery. J Paediatr Child Health 1995;31:233-6.

25. Wadhawan R, Oh W, Hintz SR, Blakely ML, Das A, Bell EF, et al.; NICHD Neonatal Research Network. Neurodevelopmental outcomes of extremely low birth weight infants with spontaneous intestinal perforation or surgical necrotizing enterocolitis. J Perinatol 2014;34:64-70.

26. Martin CR, Dammann O, Allred EN, Patel S, O’Shea TM, Kuban KC, et al. Neurodevelopment of extremely preterm infants who had necrotizing enterocolitis with or without late bacteremia. J Pediatr 2010;157:751-6.e1.

27. Allendorf A, Dewitz R, Weber J, Bakthiar S, Schloesser R, Rolle U. Necrotizing enterocolitis as a prognostic factor for the neurodevelopmental outcome of preterm infants - match control study after 2years. J Pediatr Surg 2018;53:1573-7.

28. Washbourne P. Synapse assembly and neurodevelopmental disorders. Neuropsychopharmacology 2015;40:4-15.

29. Chu J, Anderson SA. Development of cortical interneurons. Neuropsychopharmacology 2015;40:16-23.

30. Hammock EAD. Developmental perspectives on oxytocin and vasopressin. Neuropsychopharmacology 2015;40:24-42.

31. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Arlington, VA: American Psychiatric Publishing, Inc.; 2013.

32. Anveden-Hertzberg L, Gauderer MW. Surgery is safe in very low birthweight infants with necrotizing enterocolitis. Acta Paediatr 2000;89:242-5.

33. Bartels M, Althoff RR, Boomsma DI. Anesthesia and cognitive performance in children: no evidence for a causal relationship | Twin Research and Human Genetics | Cambridge Core. Twin Res Hum Genetics 2009;12:246-53.

34. Roze E, Ta BD, van der Ree MH, Tanis JC, van Braeckel KN, Hulscher JB, et al. Functional impairments at school age of children with necrotizing enterocolitis or spontaneous intestinal perforation. Pediatr Res 2011;70:619-25.

35. Salhab WA, Perlman JM, Silver L, Sue Broyles R. Necrotizing enterocolitis and neurodevelopmental outcome in extremely low birth weight infants <1000 g. J Perinatol 2004;24:534-40.

36. Simon NP, Brady NR, Stafford RL, Powell RW. The effect of abdominal incisions on early motor development of infants with necrotizing enterocolitis. Dev Med Child Neurol 1993;35:49-53.