Seminars in Fetal and Neonatal Medicine 23 (2018) 426–432

Contents lists available at ScienceDirect

Seminars in Fetal and Neonatal Medicine

journal homepage: www.elsevier.com/locate/siny

Neurodevelopmental outcomes following necrotizing enterocolitis

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ARTICLE INFO

Keywords:
Necrotizing enterocolitis
Outcomes
Neurodevelopment
Prematurity
Nutrition
Inflammation
Gastrointestinal microbiota

ABSTRACT

Necrotizing enterocolitis (NEC), a gastrointestinal emergency predominantly affecting premature infants, is associated with increased risk for poor neurodevelopmental outcomes. NEC often strikes during a period of rapid and dynamic neurologic development when the brain is particularly vulnerable to insults and nutrient deficits. The pathogenesis of neurodevelopmental impairment following NEC is likely multifactorial, with both nutritional and non-nutritional factors at play. Follow-up testing that ensures early detection and intervention for impairments is crucial to optimize neurodevelopmental outcomes following NEC. A multifaceted approach to follow-up after NEC is necessary, with close monitoring of growth, serial developmental assessments, neurologic examinations, hearing and vision testing and neuroimaging. Further research is needed to understand the pathogenesis of neurodevelopmental impairment following NEC, to identify more targeted follow-up tests, and to discover interventions aimed at optimizing neurodevelopmental outcomes following NEC.

1. Introduction

Necrotizing enterocolitis (NEC) is a common acquired life-threatening gastrointestinal condition in newborns. It primarily affects preterm born infants, occurring in approximately 10% of extremely low birth weight infants (ELBW). Surgery is required in 50–70% of these infants [1]. Despite advances in antenatal and perinatal care and increased survival rates for very low birth weight (VLBW) infants, NEC remains a potentially devastating complication for this population of infants. NEC is not only an important intestinal emergency, but it also has broader sequelae including systemic inflammation, hypoxia, ischemia, and multisystem organ failure. It can also have lasting effects beyond the acute period, including short bowel syndrome, malnutrition, re-hospitalizations, and neurodevelopmental delay.

Perinatal brain injury remains a common cause of significant long-term impairment in preterm infants. This injury can occur through a variety of mechanisms including, but not limited to, inflammation, hypoxic/ischemic injury, hemorrhage secondary to coagulopathy, and toxin exposure. Unfortunately, infants who develop NEC often additionally experience many of these complications and suffer the consequences of long-term neurodevelopmental impairment as a result. Attempts at preventing NEC and its associated brain injury have not been particularly effective. Improved understanding of the mechanisms behind this association, along with early detection and intervention for delays are therefore of utmost importance to optimize outcomes for this high-risk population. This article begins by reviewing the evidence that NEC is associated with increased risk for neurodevelopmental impairment. Then we discuss the mechanisms that likely mediate this relationship. Finally, we explore methods of neurodevelopmental monitoring after NEC.

2. NEC and neurodevelopmental impairment: a review of the recent literature

The relationship between NEC and neurodevelopmental impairment has been documented in numerous studies and systematic reviews. Several recent small matched control studies demonstrate a significant association between NEC and neurodevelopmental impairment. Soraisham et al. found that infants who develop stage II or III NEC were at significantly higher risk for the development of neurodevelopmental disability when compared to age-matched controls at 36 weeks corrected gestational age [2]. Dilli et al. demonstrated significantly lower median mental developmental index (MDI) and psychomotor developmental index (PDI) scores in a small cohort of VLBW infants with NEC compared to controls [3]. In a small cohort of VLBW survivors of NEC, Sonntag et al. found significant neurodevelopmental delay at 12 and 20 months compared to age-matched controls without NEC [4]. Salhab's group reported that a small cohort of ELBW infants with NEC had

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https://doi.org/10.1016/j.siny.2018.08.005

significantly lower mean PDI at 18 months corrected age compared to matched controls. There were no differences in MDI between groups, nor were there MDI or PDI differences between stage II and stage III NEC in this study [5].

These findings of neurodevelopmental impairment following NEC from small case–control studies are confirmed in larger, multi-center analyses, including a systematic review of observational studies reporting on neurodevelopmental outcomes of VLBW survivors after NEC performed by Schulzke et al. This review reported that the risk of neurodevelopmental impairment after one year corrected age was significantly higher in infants with NEC compared to infants who were not diagnosed with NEC [6]. Another systematic review by Rees et al. found that, when compared to age- and gestation-matched infants without NEC, infants with NEC were significantly more likely to be neurodevelopmentally impaired, specifically having increased risk of cerebral palsy, visual, cognitive and psychomotor impairment [1].

There is more inconsistency among studies when examining the question of whether infants with surgical versus medical NEC have poorer neurodevelopmental outcomes. Dilli's group did not find significant differences in neurodevelopmental outcomes between NEC survivors who required surgery and those with medically treated NEC [3]. Similarly, in a large, single-center retrospective analysis, Shah's group found that ELBW infants who develop NEC and spontaneous intestinal perforation (SIP) are at increased risk for neurodevelopmental impairment measured by Bayley testing, and there were no significant differences in neurodevelopmental outcomes observed between medical and surgical NEC groups in that study [7]. In contrast, Hintz et al. showed increased risk for adverse neurodevelopmental outcomes among infants with surgical NEC but not in infants with medically managed NEC in a large retrospective analysis. Infants with surgical NEC demonstrated increased risk for MDI < 70 and PDI < 70 on Bayley testing and the combined outcome of neurodevelopmental impairment at 18–22 months corrected age compared with infants who were not diagnosed with NEC [8]. The previously mentioned studies by Rees and Schulzke also found that surgical NEC is associated with greater risk for neurodevelopmental impairment compared to medical NEC [1,6].

Culture-confirmed infection in the neonatal period is associated with increased rates of adverse neurodevelopmental outcomes, and infants with NEC have a significantly higher incidence of culture-confirmed sepsis [9]. Martin et al. explored this relationship in a large prospective cohort study of infants included in the Extremely Low Gestational Age Newborns (ELGAN) Study. They reported increased risk of neurodevelopmental impairment, cerebral palsy and microcephaly in children who had surgical NEC, especially if they also had late bacteremia [10]. Several additional studies support this association between NEC and sepsis [2,5,7,8]. Other common complications of prematurity are reported to be associated with NEC, including longer intubation [5], chronic lung disease [2,8], intraventricular hemorrhage [7], retinopathy of prematurity [7], and longer hospital stays [2,5]. Whether a result of NEC, or an indication of the individual infant's level of vulnerability or illness above and beyond NEC, these additional complications compound risk for neurodevelopmental impairment.

Many of the studies investigating neurodevelopmental outcomes following NEC are limited by small numbers of patients from single centers. Furthermore, meta-analyses carry the challenge of generalizing the results of small individual observational studies with varied study designs, patient populations, severity of illness, management, method of follow-up and age at follow-up. Despite these limitations, the recently published literature makes a persuasive argument for the association between NEC and worsened neurodevelopmental outcomes among preterm infants (Table 1). Efforts to stratify risk for neurodevelopmental impairment by specific factors associated with NEC, including severity of illness, complications associated with NEC, and need for surgical intervention lack consensus. Large prospective studies with long-term follow-up are clearly needed to gauge the risk to long-term outcome.

Whereas the current literature demonstrates a convincing association between NEC and increased risk for poor neurodevelopmental outcomes, the specific causes underlying neurodevelopmental impairment following NEC remain to be clarified. Further understanding of the mechanisms behind these associations is an important first step in developing interventions to improve long-term outcomes for this vulnerable population.

3. Proposed mechanisms underlying associations between NEC and neurodevelopment

Late gestation and the first several years of life are periods of rapid and ongoing brain development that have been identified as “sensitive periods” of time to optimize development. The brain is composed of heterogeneous anatomical regions and functions, each with their own unique “critical period” for development. Each individual region must develop appropriately, in a time-sensitive manner, to achieve coordinated development of brain areas that work synergistically to carry out complex functions [11]. The second and third trimesters are marked by rapid brain development including neurogenesis, neuronal migration, maturation, apoptosis and synaptogenesis [12]. Infants born preterm may therefore be particularly vulnerable to factors that disrupt these processes, including malnutrition, impaired perfusion and oxygen supply, and cytotoxic mediators that accompany inflammatory processes. As a disease process that primarily affects preterm infants, the evidence of a significant relationship between NEC and neurodevelopmental disability is not surprising. It is likely that this association is multifactorial, with both nutritional and non-nutritional insults accompanying the intestinal manifestations of NEC and causing harm to the developing brain (Fig. 1). Furthermore, the timing, severity and duration of these insults will determine the specific locations of brain injury and the functional outcomes.

4. Nutritional factors affecting neurodevelopment after NEC

Nutrition plays a critical role in brain development and remains one of the few factors that the care team can manipulate. Nutrient intake recommendations for stable preterm infants are well established; however, the optimal nutritional management of infants with NEC is not well described. Infants who are diagnosed with NEC are at significant risk for undernutrition for multiple reasons. Not only do they often have compromised nutritional intake, but they may also have persistent mucosal injury following NEC that can lead to decreased absorption of nutrients. These infants often have a prolonged period without enteral feedings during the acute phase of the illness. Parenteral nutrition is the primary form of nutrition while enteral feedings are held. NEC and its treatment have the potential to induce fundamental changes in energy, protein and micronutrient metabolism that upset nutrient balance. Hyperglycemia is common and necessitates a restricted glucose infusion rate. Lipid intake, a significant source of calories when on intravenous nutrition, is often also often limited due to cholestasis related to intestinal failure, ascending cholangitis, and bile sludging following prolonged parenteral nutrition.

Whereas there is a paucity of research in preterm infants, adults who are septic demonstrate a requirement for higher energy and protein delivery due to increased cellular oxygen consumption and negative nitrogen balance [13]. Protein status is of particular importance due to its role in fat-free mass (FFM) accretion, neurogenesis, and neuronal differentiation [14]. Protein has been shown to play a role in stimulating neuronal growth factors including insulin-like growth factor-1 (IGF-1). Increased levels of IGF-1 have been associated with lower risk for abnormal cognition in preterm infants [15]. In one multicenter cohort study of infants with surgical NEC, Lin et al. reported that high protein provision in infants with surgical NEC was associated with increased head circumference, an index of brain growth [16]. Recent

Table 1
Neurodevelopmental outcomes among preterm infants.

Study	Study design	Population sample/size	NDI measurement scale	Age at follow-up	Conclusions
Sonntag et al. [4]	Matched control	20 of 22 surviving VLBW infants	Griffiths	12 and 20 months corrected age	Neurodevelopment significantly delayed in infants with NEC. 55% in NEC group had severe developmental delay compared to 22.5% of infants without NEC
Salhab et al. [5]	Matched control	17 ELBW infants with NEC	BSID 2	18 and 22 months corrected age	Compared to controls, infants with NEC had lower PDI and higher incidence of abnormal neurologic examination
Soraisham et al. [2]	Matched control	51 VLBW infants with NEC	BSID 2 and Sanford–Binet	36 months corrected age	24% of infants with NEC had one major neurodevelopmental disability compared with 10% among control infants. NEC group had significantly higher incidence cognitive index < 70 and visual impairment
Dilli et al. [3]	Matched control	20 of 39 surviving VLBW infants with NEC	BSID 2	18 and 24 months corrected age	Lower MDI and PDI in infants with NEC compared to controls; Neurodevelopmental outcomes did not differ between NEC survivors with and without surgery
Hintz et al. [8]	Multicenter, retrospective analysis	2948 ELBW infants from NICHD Research Network (245 of whom had NEC)	BSID 2	18 and 20 months corrected age	Surgical but not medical NEC was associated with adverse neurodevelopmental outcomes, including MDI < 70 and PDI < 70, at 18 and 22 months corrected age compared to no NEC
Schulzke et al. [6]	Systematic review	VLBW infants in 11 randomized studies including five studies with matched controls	Bayley or Griffiths scale	≥ 1 year	Risk of NDI significantly higher in infants with NEC compared to no NEC; risk even higher in surgical vs medically managed NEC
Rees et al. [11]	Systematic review	7843 VLBW and ELBW infants (821 with NEC)	BSID 2 and Griffiths	Median follow-up at 20 months corrected age	Infants with NEC were significantly more likely than matched controls without NEC to have NDI including cerebral palsy, visual, cognitive and psychomotor impairment; risk for neurological impairment significantly increased in stage III and surgical NEC
Shah et al. [7]	Population-based retrospective analysis	1722 ELBW infants (208 with NEC) in Cincinnati Collaborative Outreach Program Database of NICHD NRN	BSID 2	Hospital discharge, 18 and 22 months corrected age	Increased risk of NDI compared to controls; no differences in neurodevelopmental outcomes between medical NEC, surgical NEC and SIP groups

NDI, neurodevelopmental impairment; VLBW, very low birth weight; NEC, necrotizing enterocolitis; ELBW, extremely low birth weight; BSID, Bayley Scales of Infant Development; PDI, psychomotor developmental index; MDI, mental developmental index; NICHD NRN, National Institute of Child Health and Human Development Neonatal Research Network; SIP, spontaneous intestinal perforation.

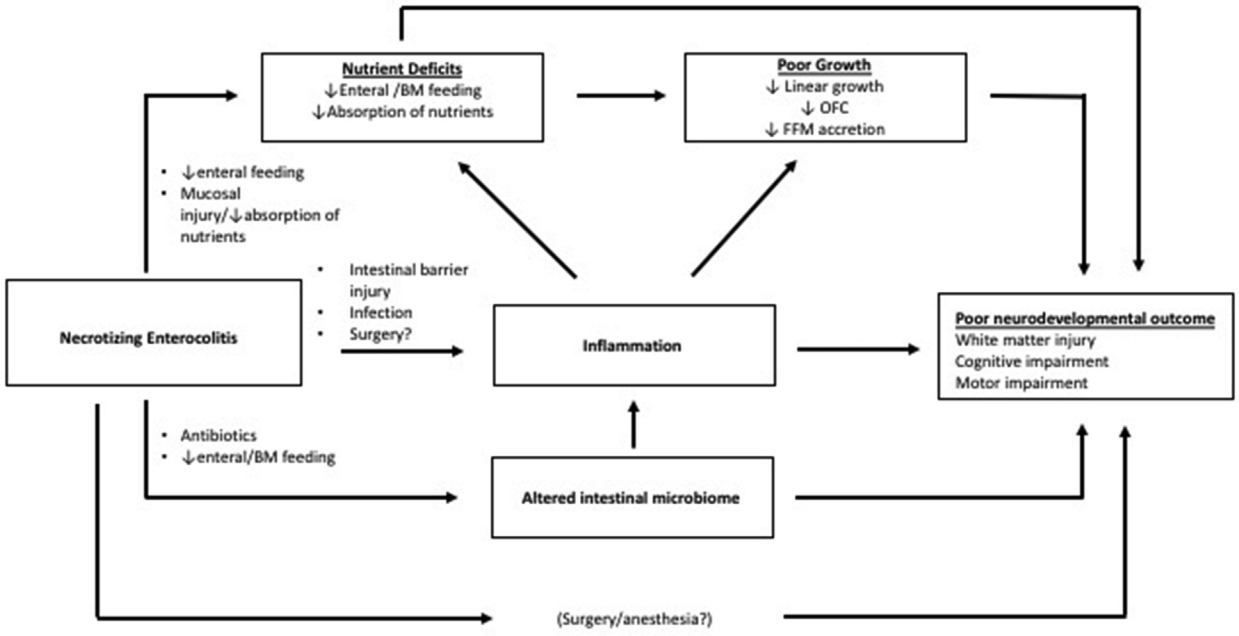

Fig. 1. Proposed multifactorial pathogenesis underlying neurodevelopmental impairment after necrotizing enterocolitis. BM, breast milk; OFC, oral feed challenge; FFM, fat-free mass.

research findings support the importance of protein in brain growth, but the value of non-protein macronutrients and micronutrients should not be discounted. Iron and zinc are two of the many micronutrients that are at risk following NEC. The absorption and trafficking of iron are significantly altered in the presence of inflammation because of the activation of hepcidin, and zinc sufficiency is jeopardized following NEC due to decreased intestinal absorption. The consequences of iron and zinc deficiency are abnormal neurodevelopment and poor growth [13]. These macro- and micronutrient deficits following NEC interfere with somatic growth and brain development during a critical period in this population of infants.

Given the importance of nutrients in brain development and the high risk for nutrient deficiencies and growth failure following NEC, further studies with the aim of optimizing nutritional management after NEC are necessary. These might include evaluation of increased protein provision following NEC. Existing studies of nutritional strategies that optimize administration of high-quality protein in preterm infants have demonstrated safety and improved outcomes [17,18]. Characterization of the ideal timing and duration of adjustments in nutrient supply to achieve continued growth and optimize neurodevelopment following NEC would also be helpful.

5. Non-nutritive factors affecting neurodevelopment after NEC

5.1. Growth and neurodevelopment

Despite attempts to optimize nutritional provision, growth failure, even in preterm infants without NEC, has been well demonstrated. As many as 79% of VLBW premature infants remain below the 10th percentile in weight at 36 weeks post-conceptual age [19]. As nutrition, growth and relationships to neurodevelopmental outcomes have been more extensively studied, the utility of growth parameters in addition to weight have been assessed. Linear growth has been identified as an important indicator of FFM accretion and a potential marker of future cognitive deficit in VLBW preterm infants [20]. Even in infants without NEC, linear growth failure persisting beyond the second year of life is common [21,22]. Accurate linear growth measurements are difficult to obtain, and, more recently, some centers have used air-displacement plethysmography to non-invasively measure body composition in infants. Studies using body composition measurements reveal that the quality of growth in preterm infants is altered, with decreased amounts of FFM and increased adiposity noted at term corrected age, specifically in those infants who were more critically ill [14,21,23,24]. Because of the pervasive nature of postnatal growth failure in preterm infants, its consequences, including associations with poorer neurodevelopmental outcomes, have been well documented [22,25,26].

Compared to their healthy counterparts, sick neonates are at even higher risk for growth failure and neurodevelopmental impairment [13]. The underlying etiology of growth failure and risk for poor neurodevelopmental outcome following NEC is likely multifactorial. Difficulty feeding during the acute stage of the illness and resultant malnutrition seems to provide a credible but incomplete explanation. Both inadequate nutritional delivery and other non-nutritional mechanisms such as inflammation and key changes in cellular metabolism that alter nutrient demand, availability, and handing are likely also at play in the observed changes in growth and development [13,27]. A series of physiological changes, involving inflammatory factors and hormones, in response to the stress of an acute illness promotes short-term survival but is likely detrimental to long-term growth and development [21]. Alterations in the growth hormone (GH) axis have been suggested in the relationship between illness and risk for poor growth and neurodevelopmental outcomes. Critically ill children become relatively GH resistant and demonstrate elevated GH levels with inappropriately low IGF-1 levels [20,28,29]. As discussed previously, higher IGF-1 levels have been associated with improved neurodevelopmental outcomes [15].

Although we may be able to extrapolate some findings from studies of other illnesses, follow-up studies on long-term growth and its association with neurodevelopmental outcomes specifically following NEC are few, and the results are inconsistent. Hintz et al. reported significant growth failure only in ELBW infants with NEC requiring surgical treatment but not in infants treated medically for NEC compared to controls. Two other studies did not find any significant differences in weight, length, or head growth between NEC survivors and control infants without NEC [3,4]. Further studies of growth, inflammation, and hormonal changes are warranted to better understand the role of non-nutritional factors in growth and neurodevelopmental outcomes following NEC.

5.2. Inflammation and neurodevelopment

Increased levels of local tissue and circulating pro-inflammatory cytokines are involved in the pathogenesis of NEC. In one hypothesis, intestinal injury and barrier dysfunction permit translocation of inflammatory mediators and bacteria into systemic circulation, resulting in a systemic inflammatory response. The observation that increased disease severity (i.e. more significant injury to the intestinal barrier and resultant systemic inflammation) is associated with adverse neurodevelopment supports this theory [7]. Ubiquitous signaling molecules with pro-inflammatory, anti-inflammatory, trafficking, growth, and damage repair roles, including cytokines, chemokines, and growth factors are implicated in the relationship between infections distant from the brain and brain injury [30]. In a multicenter study of infants affected by NEC, increased serum levels of pro-inflammatory cytokines were found to be associated with increased risk for poor growth and development [31]. A similar phenomenon occurs with maternal and/or neonatal inflammation or infection, as these infants have also been shown to be at higher risk for long-term neurodevelopmental impairments, in particular cerebral palsy, in several cohort studies and a meta-analysis of these studies [32].

White matter injury, often manifested as periventricular leukomalacia (PVL), is an important example of disrupted brain development and neurologic disability in preterm infants [33]. The underlying pathogenesis of cerebral white matter injury involves cerebral ischemia, systemic infection or inflammation, and intrinsic vulnerability of cerebral white matter pre-myelinating oligodendrocytes, particularly around 28–32 weeks gestation. Also peaking during this high-risk gestational period is cerebral microglial activation, which becomes heightened in the context of systemic inflammation and contributes to ongoing injury [34]. Observational studies have shown an association between PVL and maternal intrauterine infection with fetal systemic inflammation or neonatal systemic infection with neonatal systemic inflammation [32,35,36].

5.3. Intestinal microbiota, inflammation, and brain development

The role of the intestinal microbiota in the prevention, pathogenesis, and potentially the neurodevelopmental consequences following NEC deserves mentioning here. The gut microbiota, a diverse and complex community composed of trillions of microbes, is known to play an important role in the developmental programming of gut epithelial barrier function and the gut immune system. Recently, new studies have shown an important link between the microbes that inhabit the intestinal tract and the developing brain [37].

Knowledge of the factors that influence the neonatal gut microbiota has greatly expanded in the last few decades. The intestinal microbiota of the neonate appears to be highly sensitive to maternal health status, antenatal infection, antibiotic exposure and preterm birth [37]. The infant's mode of delivery, type of nutrition and early use of antibiotics alter the composition of the gut microbiota and may have long-lasting effects [38]. Exposure to antibiotics early in life has been shown to significantly alter the development of the neonatal gut microbiota. In fact, there is evidence that antibiotic treatment causes more drastic and sustained changes to the gut microbiota when compared to other clinical factors [39–41].

The local damage to the intestine, withholding of enteral feedings and antibiotic treatment that accompany NEC all pose significant risk for a perturbed gut microbiota in the infants who suffer from this disease process. An altered intestinal microbiota may intensify inflammation, potentiate intestinal barrier dysfunction and delay healing. Furthermore, a perturbed gut microbiota has the potential to influence neurodevelopmental outcomes via inflammation and possibly has a direct effect on the central nervous system. Recent animal model studies exploring the link between an altered gut microbiota and brain development have uncovered evidence for potential mechanisms underlying this relationship, including changes in expression of genes and proteins involved in neurotransmission, synaptic plasticity and metabolism, control of stress hormones, or neuronal signaling via the vagus nerve [42]. Further studies are needed to determine whether these relationships exist in humans and to explore the functional consequences of these potentially important physiological changes associated with an altered gut microbiota.

5.4. Other factors

The observation that infants with surgical NEC have increased risk of poor neurodevelopmental outcomes raises the question of whether this association could be related to a heightened inflammatory response following surgery, the possibility of anesthetic-related neurotoxicity, or the severity of the disease process (need for surgery indicating advanced NEC). In addition, the type of surgery performed may play a role in long-term outcomes, including neurodevelopment. In a multicenter cohort study comparing initial laparotomy and peritoneal drain placement in ELBW infants with NEC, a risk-adjusted odds ratio for death or neurodevelopmental impairment favored laparotomy over peritoneal drain placement [43]. This may be due to the potential for needing a second surgery, prolonged courses of nil-per-os and/or antibiotics or other undetermined factors. Additional studies comparing laparotomy and peritoneal drain placement focus on outcomes of mortality, rates of dependence on enteral feeding and duration of hospital say and are inconclusive. Large, multicenter randomized controlled trials including neurodevelopmental and growth outcomes are needed. The question of anesthetic-related neurotoxicity is also unsettled. In animal models, anesthetics have been found to increase neuronal cell death following exposure. Subsequent neurologic abnormalities have been noted in some studies. Translation of these findings from animals to humans is problematic and observational studies of children exposed to surgery are conflicting [44].

Adding yet another facet to the hypothesis of a multifactorial process mediating the relationship between NEC and neurodevelopment, it has been proposed that NEC pathophysiology may only be a small part of, or simply a maker for, other risk factors. For example, the bowel immaturity that predisposes an infant to NEC may be an indicator of brain maturity and vulnerability beyond that attributed to gestational age. NEC may simply be a marker of illness severity during an infant's NICU stay [7]. Regardless of the exact role that NEC itself plays in the risk for poor neurodevelopmental outcomes, infants who are affected by this disease require close follow-up.

6. Neurodevelopmental follow-up after NEC

While studies in the prevention of NEC and its long-term sequelae are ongoing, the interventions with the highest likelihood of improving outcomes related to this potentially devastating disease remain in vigilant follow-up, monitoring and serial assessments with the goal of early detection of impairments and prompt intervention.

6.1. Clinical monitoring and neuropsychological assessment

Although they are not a direct measure of brain development, anthropometric measurements, including weight gain, linear growth and head circumference, are important components of follow-up for a preterm infant affected by NEC. Linear growth reflects lean body mass and protein accretion. It correlates with brain growth, making it an important biomarker to predict long-term developmental outcomes in VLBW infants [21]. Studies in the use of body composition in preterm infants show that increased early FFM gains are associated with improved neurodevelopmental outcomes, including higher cognitive and motor scores, faster speed of processing, improved working memory, and higher IQ [24]. Since the “critical period” of brain development extends until about three years of age, correction of growth failure in

the first few months to years of life, or better yet prevention, can improve neurodevelopmental outcomes. Frequent monitoring of easily obtainable growth measures can ensure identification and prompt interventions with a higher likelihood of optimizing neurodevelopmental outcomes.

The Bayley Scales of Infant Development (BSID) is a widely used tool in assessment for neurodevelopmental delay. This standardized developmental test is important in early detection of developmental delay; however, in determining need for early intervention programs and evaluating treatment effectiveness, it is not without limitations. Poor predictive value of early testing for cognitive impairment at school age and underestimation of delays are cited limitations of the BSID-II and BSID-III, respectively [45,46]. These assessments are best applied serially and used in conjunction with regular thorough neurologic examinations to assess the quality of motor skills, coordination, gait and behavior in addition to hearing and vision evaluation by appropriate professionals.

One aspect of brain development that is likely to be affected by prematurity, poor nutrition and growth is speed of neuronal processing, due to effects of these insults on the processes of synaptogenesis and myelination. Speed of processing can be assessed as soon as early infancy with visual evoked potentials (VEPs), which are time-locked electroencephalographic recordings representing the brain's response to a specific visual stimulus. Although VEP is not currently used broadly in non-research settings, it may give some insight into early postnatal brain development and provide a clearer connection between neonatal risk factors and brain function. More research is needed to identify specific testing modalities that can reliably identify impairments in the areas of the brain that are still developing, and therefore particularly vulnerable at the time when NEC and its associated insults occur.

6.2. Neuroimaging

Cranial US (CUS) is currently the most widely used neuroimaging technique in this population. It is an ideal mode of imaging to detect intraventricular hemorrhage and cystic PVL; however, it has limited value in detecting diffuse white matter injury in studies comparing neonatal ultrasonography with magnetic resonance imaging (MRI) [47,48]. The role of MRI in neonatal care has been increasingly investigated in the last decade as a potential tool to assist in early prognostic evaluation.

Several studies evaluating the prognostic power of MRI for prediction of neurodevelopmental abnormalities have been performed in preterm infants, a population with high risk for neurodevelopmental impairment (even in the absence of NEC). Both late CUS and near-term MRI abnormalities were associated with adverse neurodevelopmental outcomes at 18–22 months corrected age in a cohort of infants with birth gestational age < 28 weeks in the Neonatal Research Network. Early CUS findings were not associated with adverse outcomes. This same study also reported that a considerable number of children with late CUS or MRI findings did not have significant adverse neurodevelopmental outcomes [33].

Another recent observational study of preterm infants found significant associations between cerebral white and gray-matter abnormalities on MRI at term equivalent age and risk of adverse neurodevelopmental outcomes at two years of age. Moderate-to-severe cerebral white-matter abnormalities on MRI at term equivalent age were predictive of severe cognitive delay, severe psychomotor delay, cerebral palsy, and neurosensory impairment. Gray-matter abnormalities were also associated with increased risk of cognitive delay, psychomotor delay, and cerebral palsy, but less so compared to white-matter abnormalities. Risk predictions from these MRI findings were independent of other perinatal factors and abnormalities on cranial ultrasonography [49].

The usefulness of MRI as a diagnostic tool to assess brain development and injury, either alone or in addition to information available through physical exam, developmental testing, and other imaging, remains to be elucidated. Before this becomes standard practice, there needs to be more clear determination of practical considerations such as ability to acquire images without sedating medications. In addition, whereas abnormal findings are often associated with long-term disability, some infants develop without significant disability despite abnormalities on neuroimaging. Neuroimaging may serve as a helpful tool in predicting neurodevelopmental outcome, but long-term follow-up to understand the evolution of brain injury over time and assess functional outcomes is necessary.

7. Conclusions

In summary, NEC remains an important, life-threatening illness that primarily affects preterm infants and can have life-long complications. Infants with NEC are at increased risk for poor neurodevelopmental outcomes, a relationship that is likely multifactorial, including nutritional and non-nutritional factors. Survivors of NEC require long-term follow-up to monitor for signs of neurodevelopmental impairment to ensure prompt intervention.

7.1. Practice points

- Current evidence indicates that the diagnosis of NEC is associated with increased risk for neurodevelopmental impairment; for infants with a history of NEC, long-term follow-up, early diagnosis and intervention are critical to improving and optimizing long-term neurodevelopmental outcomes.
- There is not one follow-up test that alone can reliably predict risk for neurodevelopmental impairment currently; instead, a combination of testing methods provides the best risk stratification.
- Most neurodevelopmental follow-up studies are performed at young ages and may not represent true long-term outcomes; longitudinal follow-up beyond preschool age is necessary.

7.2. Research directions

- Randomized trials aimed at improving nutrition, decreasing systemic inflammation and preserving the intestinal microbiota would promote improved understanding of the pathogenesis underlying the relationship between NEC and poor neurodevelopmental outcomes, and inform possible preventative measures.
- There is a need for prospective, longitudinal follow-up studies after NEC, exploring specific assessments of brain areas that are known to be developing rapidly in the third trimester to assist in the precise targeting of interventions to optimize outcomes.

Conflicts of interest

None declared.

Funding sources

None.

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