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Research Article

Expanding the Necrotizing Enterocolitis Spectrum Disorder: A Single Center's Experience

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Abstract

It has been proposed that necrotizing enterocolitis [NEC] is not one disease, but rather the final common pathway along a clinical spectrum.

Aim: We aimed to examine the hypothesis that early NEC in extremely low gestational age [ELGA - GA ≤ 28 weeks] neonates constitutes a new category on the NEC spectrum. Classical NEC presents after 2 weeks and peaks at 32 weeks.

Setting and Design: Retrospective review.

Results: We identified 16 ELGA infants with early NEC confirmed by pneumatosis and/or pathology. They presented at 7±3 days and 27±2 weeks, well below the classically described NEC. Although seven infants presented with perforations, they were not spontaneous intestinal perforations (SIPS) in that all had clearcut pneumatosis and/or bowel necrosis on pathology. Mortality was 50%.

Conclusion: We propose that NEC should be viewed as a spectrum disorder and that early NEC in the extreme preterm neonate constitutes a distinct category of NEC along this spectrum with high mortality and different pathophysiology.

ABBREVIATIONS

NEC: Necrotizing Enterocolitis; ELGA: Extremely Low Gestational Age; SIP: Spontaneous Intestinal Perforation

INTRODUCTION

Necrotizing enterocolitis [NEC], is a leading cause of gastrointestinal morbidity among premature neonates [1]. Clinical diagnosis, however, remains challenging as initial signs and symptoms can lack both specificity and sensitivity. Gordon et al. [2,3], suggested re-defining NEC as a spectrum disorder, with overlapping, yet distinct, subsets. Distinguishing these separate entities offers potential for more directed therapy.

Based on our experience in a single large center with over 20,000 deliveries/year, we would like to propose an additional element along this spectrum – early NEC in extremely low gestational age (ELGA) infants. Classical preterm NEC presents at >2 weeks and 32 weeks postmenstrual age (PMA) [4,5]. Recently, we have cared for a series of ELGA infants with fulminant NEC presenting within the first week of life. While early NEC is well described, it typically occurs in more mature, term or late preterm neonates. Yoffe Deri et al. [6], proposed that early onset NEC has significantly different clinical and microbiological attributes when compared with late onset NEC. Spontaneous isolated intestinal perforations (SIP) also occur early, but are distinct in that the mucosa surrounding the perforation is healthy. SIP can only be definitively diagnosed at surgery [7]. We propose that early NEC in ELGA neonates constitutes a distinct category along the NEC spectrum. Although differences between NEC subtypes may be subtle, they can be clinically important.

METHODS

We retrieved the records of all ELGA babies hospitalized in the Shaare Zedek Medical Center between 2016-2019 with NEC occurring <2 weeks of age. Only infants with clear-cut pneumatosis on x-ray and/or bowel necrosis on pathology were included, thereby eliminating SIPs

RESULTS

We identified 321 ELGA infants; 25 of whom developed NEC prior to 2 weeks. Nine were excluded- four re-classified as probable SIPs; two with complex congenital heart disease; and

three were diagnosed clinically as NEC but lacked pneumatosis on x-ray and/or definitive pathology results (no surgery).

Sixteen extremely preterm infants with early confirmed NEC remained. They were 26.3±1.9 wks and 930±302 grams at birth. Two received pRBC transfusions within 48 hours of the NEC onset; two were thrombocytopenic; two were CMV negative during NEC and turned positive a month later. All were on antibiotics. Four infants had positive placental cultures and four others had positive peritoneal fluid cultures. Candida cultured from one peritoneal swab.

Classical preterm NEC presents at a mean postnatal age of 2 weeks and PMA of 32 week. In our infants, NEC presented at 27±2 weeks and 7±3 days of age, significantly earlier than classical preterm NEC. Nine were fed mother's milk exclusively; four had reached full feeds.

Nine infants presented with bloody stools and seven with perforation. Most had mild (≤3 cm) abdominal distention, although three had increases in abdominal girth of >4 cm. All of these three had perforations.

Although seven of the infants presented with intestinal perforations, they differed from SIPs in that all had clearcut pneumatosis on x-ray and/or evidence of bowel necrosis on pathology. Nine did not perforate, thus did not even raise suspicion of SIP. Mortality was 50%.

DISCUSSION

We propose viewing NEC as a spectrum disorder, and that "Early preterm NEC" represents a distinct sub-category along the NEC spectrum, distinct from classical NEC in its very early presentation in ELGA neonates, in the predominance of exclusive breast feeding and in its high mortality. Affected infants had documented bowel necrosis, distinct from SIP. Table 1, modified from Gordon [4], summarizes the NEC spectrum and including the new sub-group. It further demonstrates that our infants do not fit neatly into any of the other categories.

NEC has consistently been characterized by a strong inverse relationship between gestational age at birth and time of disease onset. NEC in full-term infants typically develops within the first few days of life, whereas NEC in preterm infants of less

Table 1: NEC Spectrum Disorders.

	Traditional Preterm NEC	Early Preterm NEC	Spontaneous Intestinal Perforation (SIP)	Food protein-induced enteroco-litis (FPIES)	Viral Enteri-tis	Term NEC	Transfusion Asso-ciated NEC
Postnatal Age	>2 wks	<2 wks	< 2 wks	Variable; usually >2 wks	>2 wks	<2 wks	>2 wks
Risk Factors			Dexa-metha-sone, NSAIDs	Exposure to cow milk protein	Exposure to virus (rotavi-rus; entero-virus; CMV)	Some antecedent condition; Hypoxic/ ischemic event; complex congenital heart disease; IUGR; polycythemia	pRBC transfu-sion; anemia
Pneumatosis	Yes	Yes	No	Rare	Common	Yes	Yes
Pneumoperitoneum	20-30%	45%	100%	No	30-40%	Rare	Rare
Bloody Stools	Common	Common	Variable	Variable	Common	Common	Common
Feeds (ml/kg/day)	>80	Variable; usually <80	<40	<80	>100	>100	Possible/ contro-versial association with feeds during transfusion
Clinical presentation	Abdominal distention (70-98%); feeding intolerance (70%); bloody stools (25-63%). Although pneumoperito-neum may ensue in about 1/3 of patients, rarely a presenting sign	Abdominal distention; feeding intolerance; bloody stools; pneumoperito-neum	Free air	Abdominal distention; bloody stools	Bloody stools	Bloody stools	Bloody stools

Mortality	30%	50%	20-40%	<20%	14%	13% (Lambert. Necroti-zing enterocolitis in term neonates)	>50%
Surgical Pathology	Pneumato-sis with mucosal necrosis	Pneumato-sis with mucosal necrosis	Focal perforation with robust surround-ing mucosa	None	Ascites, bowel necrosis	Pneumato-sis with mucosal necrosis	Pneumato-sis with mucosal necrosis

than 29 weeks' gestational age has symptom onset at several weeks of life, typically at 30 to 32 weeks postmenstrual age[7]. A recent white paper from the International Neonatal Consortium (INC) suggests considering an alternative diagnosis in preterm infants who develop pneumoperitoneum at less than 10 days of life [8,9].Yee et al. [4], described a bimodal distribution of NEC onset, with early NEC at ~8 days of age in late preterm infants (quite distinct from our ELGAs), and a second peak in smaller preterms at ~19 days. Postnatal day 14 was defined as the cutoff between early and late NEC. González-Rivera et al[5] found that GA alone accounted for 42% of the age difference in NEC onset. This approach to timing has even been used as a diagnostic criterion in NEC studies [10]. NEC presentation peaks at ~32 weeks PMA. The babies described here do not fit this classical timing paradigm. Given their early gestational ages, these babies should not have developed classical NEC until approximately six weeks postnatally.

Our group is also inconsistent with other described NEC subgroups. Differentiation from SIP has already been discussed. Food protein-induced enterocolitis (FPIES) reflects hypersensitivity to food antigens. It occurs in older infants, typically 1-4 weeks after exposure to formula rather than human milk [10]. It is not associated with perforation or with mortality. Case reports have identified an association between CMV infection and neonatal gastrointestinal pathology including enterocolitis. Panesso-Gomez detected CMV in intestinal tissue from 4% of NEC and 3% of SIP cases [11]. None of our infants had CMV at the time of NEC. Finally, the possibility of an association between recent exposure to pRBC transfusion and development of necrotizing enterocolitis (TANEC) has been proposed [12]. However the existence of this entity remains controversial.

In summary, we present a retrospective review, suffering from the limitations inherent in any retrospective, single center review. Is this really a new subset in the NEC Spectrum? Definitive classifications are complex and inherently inaccurate when dealing with human infants. There will often be overlap between subsets. So it is reasonable to ask whether we are merely seeing cases at the extreme end of classical NEC. Yet Gordon's approach to NEC opts for delineating subsets rather than an inclusive continuum. If confirmed by further observation, this group with its high mortality may warrant more aggressive clinical management strategies.

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AUTHORS' CONTRIBUTIONS

Alona Bin-Nun made substantial contributions to the conception and design of the work and to the acquisition of data.

Yair Kassirer substantial contributions to the conception of the work and to the acquisition of data.

Irina Shchors made substantial contributions to the data acquisition,

Cathy Hammerman made substantial contributions to the conception and design of the work; to the acquisition, analysis, and interpretation of data and drafed the manuscript.

All authors reviewed and approved the final version of the manuscript.

ETHICS

The study was approved by the local institutional review board in accordance with the World Medical Association Declaration of Helsinki. As a retrospective review of unidentified subjects, parental consent was not required.

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