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Pathophysiology 21 (2014) 21–27

ISP PATHOPHYSIOLOGY

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Decoding the enigma of necrotizing enterocolitis in premature infants

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Abstract

Necrotizing enterocolitis (NEC) is an enigmatic disease that affects primarily premature infants. It often occurs suddenly and when it occurs, treatment attempts at treatment often fail and results in death. If the infant survives, there is a significant risk of long term sequelae including neurodevelopmental delays. The pathophysiology of NEC is poorly understood and thus prevention has been difficult. In this review, we will provide an overview of why progress may be slow in our understanding of this disease, provide a brief review diagnosis, treatment and some of the current concepts about the pathophysiology of this disease.

Keywords: Necrotizing enterocolitis; Preterm infant; Prevention

1. Introduction

Necrotizing enterocolitis (NEC) has been reported since special care units began to house preterm infants .With the advent of modern neonatal intensive care approximately 40 years ago, the occurrence and recognition of the disease markedly increased [1]. It is currently the most common and deadly gastrointestinal illness seen in preterm infants. Despite major efforts to better understand, treat and prevent this devastating disease, little if any progress has been made during these 4 decades. Underlying this lack of progress is the fact that what is termed "NEC" is likely more than one disease, or mimicked by other diseases, each with a different etiopathogenesis. The comprehensive inclusion of these entities into datasets used for epidemiologic studies has likely diluted the associative signals; hence blurring the utility of the information that can be derived. Further confusing this issue is the use of animal models for over 3 decades that are poor representatives of the disease seen most commonly in preterm infants. Approaches have also been used that evaluate tissue from patients with NEC in an attempt to better define the pathophysiology, but this most often represents dead or dying tissue removed by the surgeon and thus is a poor representation of the proximal events of the disease, which need to be the focus of our work, since these are the components of the disease where intervention or preventative measures could be most effective.

In this review, the focus will be on the most common form of NEC seen in preterm infants, but some discussion of the other entities termed "NEC" will be briefly presented.

2. "NEC": the mimickers

Some examples of disease entities that can mimic NEC are seen in Table 1. Term or near term infants with "NEC" when compared to matched controls usually have occurrence of their disease in the first week after birth, have a significantly higher frequency of prolonged rupture of membranes, chorioamnionitis, Apgar score <7 at 1 and 5 min, respiratory problems, congenital heart disease, hypoglycemia, and exchange transfusions [2]. When a "NEC" like illness presents in term or near term infants, it should be noted that these are likely to be distinct in pathogenesis than the most common form of NEC and should be differentiated as such.

2.1. Primary ischemic necrosis

All cases of "NEC" have necrosis as a final endpoint by definition. However, primary intestinal ischemia due to low flow states in the large vessels supplying the intestine

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http://dx.doi.org/10.1016/j.pathophys.2013.11.011

Table 1
Examples of disease entities that mimic NEC.

Entity	Time of presentation	Primary intestinal ischemic injury	Intestinal region involved	Term/preterm
Ischemic bowel disease with congenital cardiac disease	First week	Yes	Entire bowel	Usually term but can also be seen in preterms. Occasionally also seen in intrauterine growth restricted infants with reverse diastolic mesenteric blood flow
Hirschprung's disease	First week	No	Colon is most common	Usually term but can also be seen in preterms
Spontaneous intestinal perforations	First week	May be related to previous in utero insult but unclear and usually not directly associated with thrombotic or low flow acute ischemia, except possibly in association with indomethacin use when combined with glucocorticoids	Ileum is most common	Usually in very small preterm infants
Cow's milk protein protein allergy	First couple of weeks	Etiology poorly understood because immune system poorly developed	All regions may be affected	Term and near term. Usually a relatively benign presentation

is not the primary event in the majority [3]. Many of the infants who suffer primary ischemic necrosis are term or near term infants (although this can occur in preterms) who have concomitant congenital heart disease, often related to poor left ventricular output or obstruction. Other factors that have been associated with primary ischemia are maternal cocaine use, hyperviscosity caused by polycythemia or a severe antecedent hypoxic–ischemic event. Whether the disease entity that results from this should be termed NEC can be debated on historical grounds, but the etiology is clearly different from the NEC seen in most preterm infants.

2.2. *Congenital bowel abnormalities: Hirschsprung's disease*

In a study wherein rectal biopsies were performed in infants weighing >2400 g, who developed "NEC" without other obvious causes, over 50% were shown to have aganglionosis (long segment Hirschprung's disease) when rectal biopsy was performed [4].

2.3. *Spontaneous intestinal perforation*

Another entity that mimics NEC is referred to as spontaneous intestinal perforation (SIP). SIP in preterm infants was first reported in six very low birth weight infants. In all cases the clinical and radiographic presentations, as well as the histologic findings, were distinct from those associated with necrotizing enterocolitis [5]. Most of these cases occur very early (usually in the first week after birth) and in very preterm infants. Spontaneous intestinal perforation (SIP) is associated with the combined use of postnatal glucocorticoids and indomethacin in extremely low birth weight (ELBW) infants [6]. These infants frequently have never been fed or are only being fed minimal quantities. The affected intestine most commonly presents with minimal or no necrosis and single perforation in the ileum.

2.4. *Miscellaneous*

Several other mimickers of NEC occur, but are poorly understood. These include intestinal pathology associated with neonatal cow's milk protein intolerance [7], use of milk thickeners ("Simply Thick") [8], blood transfusion [9] and octeotride administration [10]. Infants with neural tube defects [11] are at higher risk for a "NEC" like disease. But as with the others, the etiology is poorly understood.

3. Clinical presentation of "classic" NEC

The remainder of this review focuses on the most common form of the disease, which involves an inflammatory intestinal condition in prematurely born infants. The more premature the infant, the later this condition occurs after birth [12–14]. The initial signs and symptoms of "classic" necrotizing enterocolitis in a preterm infant most often include feeding intolerance, abdominal distention and bloody stools