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NARRATIVE REVIEW

Recovering the "lost thread" in the "skein" of necrotizing entero-colitis of newborns.

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Abstract

Purpose of the review: The objective of this review is to delineate the pathophysiology of the classic Entero Necrotizing Colitis (NEC) of newborns, propose a list of perinatal antecedents that define a risk group, and establish simple and objective parameters that help to establish an early clinical diagnosis.

Recent findings: The mortality of the classic NEC of newborns is still high. Although the disease has several presentations, it is unique with a single installation route, and intestinal hypoperfusion is the initial offending agent.

Excerpt: The lack of prevention strategies and very late clinical diagnosis explain the high mortality of NEC. There is great confusion about the origin of the disease, implying that there are different types of NEC. Although the disease is unique, it has different manifestations according to the conditions of the newborn with a common route of installation, with intestinal hypoperfusion as an initial assailant agent. This article postulates that recognizing intestinal hypoperfusion as the initial offending agent is "finding the lost thread" that could help in developing prevention and treatment strategies, identifying patients at risk of NEC, and achieving a diagnosis early.

Keywords: Enterocolitis; Enterocolitis, Necrotizing; Infant, Newborn; Infant, Premature; Diving Reflex; Endotoxemia; Gastrointestinal Hemorrhage.

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Introduction

Necrotizing enterocolitis (NEC) of newborns is an acute, acquired, severe, inflammatory, infectious, potentially fatal bowel condition. The evolution is influenced by the clinical conditions of the newborn. It is the most frequent cause of acute abdomen in this age group, it particularly affects premature infants, and it carries a high mortality with a slight decrease over time according to a recent publication by Han and Knell [1].

The etiopathogenesis is still controversial [2]. We compare the current postulates about the disease to a skein, whose initial "thread" has become so confusing that we consider it "lost." We theorize that the disease presents a common pathway of initiation, which is the "immersion reflex" (IR) [3, 4], with the resulting mesenteric hypoperfusion as a common agent of initial aggression. By altering the natural barrier function of the intestinal mucosa, it triggers a sequence of pathophysiological events, leading to the classic NEC.

This common pathway of installation of the disease is preceded by many risk factors of inducing the "immersion reflex," the presence of which identifies patients at risk of disease. The sequence of pathophysiological events presents clinical manifestations, laboratory signs, and radiological signs. When properly ordered, these signs can establish an earlier clinical diagnosis earlier. The recognition of patients at risk and the establishment of an early diagnosis is the "lost thread" that we must recover.

Discussion

The intestinal areas most frequently affected are the terminal ileum, the cecum, and the sigmoid colon [5]. Characteristically, histopathology shows mucosal necrosis with loss of villi and hemorrhagic necrosis with vascular (ischemic) thrombosis of the intestinal wall submucosa [5-7]. Its pathophysiology is still controversial with several inconsistent theories in many respects. It is speculated that it involves several factors, such as intestinal prematurity, altered intestinal microbiota, immature innate or acquired immune response capacity of the NB, and the initiation and type of enteral feeding.

Adverse effects of dive reflex

It is proposed that NEC is a sequence of events triggered by mesenteric hypoperfusion caused by IR [3-4]. RdI consists of breath holding, vasoconstriction, and a drop in heart rate in response to immersion of the face in cold water. This reflex occurs in all mammals as a physiological and survival reflex. It produces peripheral vasoconstriction, which includes the splanchnic area, to preserve the irrigation of the vital organs and thus preserve life.

It is suggested that this protective reflex presents adverse effects when it occurs in newborns. The adverse results are inversely related to the perinatal conditions of the NB and the diameter of the mesenteric arteries. The sequence that develops results in intestinal hypoperfusion (mild, moderate or severe) and alters and/or damages the intestinal mucosa (which is considered a natural balance barrier). This is followed by the translocation of Gram (-) bacteria and endotoxins, which cross the mucosal barrier and stimulate the TLR-4 response in the intestinal wall. This in turn initiates the inflammatory cascade of cytokines, worsening the poor perfusion of the intestinal wall and causing necrosis, perforation, peritonitis, and sepsis.

Activation of TLR-4 as a consequence of mucosal injury

The theory supported by some authors [8-9] is that the inflammation resulting from bacterial colonization is what damages the intestinal mucosa. Hackam [6] reviewed the pathophysiology from a historical context and stated, "... when the intestine of a premature infant is colonized by bacteria, particularly Gram (-), the activation of TLR-4 leads to mucosal lesion, decreased capacity to repair the mucosa, and bacterial translocation, which in turn causes vasoconstriction, producing necrosis of part of the intestine, which is the characteristic of NEC ." This suggests that the TLR-4 is activated by the presence of certain pathogenic bacteria in the intestinal lumen.

With this new hypothesis, it is relevant to pose the following questions: is TLR-4 activated only by the presence of Gram (-) bacteria in the intestinal lumen? Or is it activated when the immune system comes into contact with bacteria and endotoxins that cross the

mucosa? According to the concept proposed in this article, all "reactions" occur as a response to an initial "action or aggression" and not spontaneously. Thus, it is interpreted that TLR-4 is activated as a consequence of the mucosal injury, which allows translocation.

Traditional etiopathogenic factors aggravate the course of NEC

The different factors considered etiopathogenic in the context of this new hypothesis participate not as independent causes producing different types of NEC, but rather, these factors aggravate the clinical course of the adverse effects of mesenteric hypoperfusion caused by RoI. It is recognized that multiple bacterial colonizations of the NB's intestinal tract occur in all NBs within the first hours of life [10], regardless of the condition at birth. These bacteria remain in equilibrium while the natural barriers are intact as long as there is no mucosal injury.

Although dysbiotic bacteria are found primarily in the distal intestine, they are not exclusively in the large intestine. Dysbiosis is a regional factor that includes the entire gastrointestinal tract. If dysbacteriosis were occurring, it would be established as an independent cause of an NEC type, and it would not be explained why the intestinal areas most frequently affected are specifically the terminal ileum, the cecum, and the sigmoid colon. But considering that these anatomical areas are irrigation territories of the terminal branches of the mesenteric arteries, it is easily understood that these are the areas most affected in the course of NEC.

Dysbacteriosis per se does not explain the histopathological characteristic of ischemic necrosis of the intestinal wall in all cases of classic NEC. Considering that the initial offending agent is intestinal ischemia due to mild, moderate, or severe mesenteric hypoperfusion, depending on the intensity of the IR, dysbacteriosis has great relevance, and if it does not exist, it is very possible that the effects of mild, moderate, or severe hypoperfusion go unnoticed against saprophytic intestinal flora.

The same argument raises the inconsistency of the theory that other factors (gestational immaturity, inadequate immune reaction, and the initiation of enteral feeding) are independent etiopathogenic factors that cause different pathological entities and suggest NEC in premature and premature infants. Term NBs are different diseases, as is NEC, regardless of whether it is related or not to cyanotic heart disease [11].

Following this line of thought, a hypothesis is established that NEC is a single entity in all patients and has a common route of installation with tissue hypoxia as the initial offending agent, whose effects may be aggravated by the different factors considered and are reported by others as etiopathogenic. We postulate that by recognizing the perineal factors that signify stress to the fetus and the risk of inducing IR, we will be

Fig. 1 Demarcation of the abdominal girth measurement site. Average distance between pubic bone and xiphoid process.

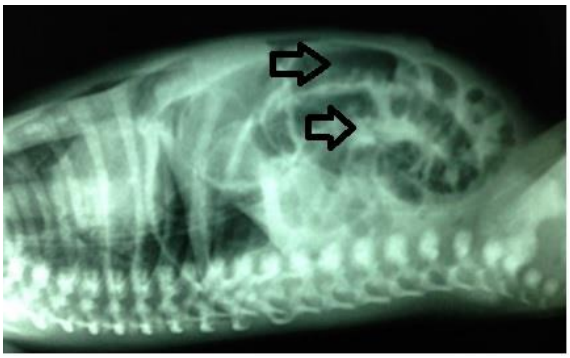

Fig. 2 Upper arrow indicates bowel loop dilation; the lower arrow indicates the edema of the intestinal wall.

able to identify the group of patients who are at particular risk of generating the "diving reflex" with the consequent mesenteric hypoperfusion [12, 13]. Perinatal risk factors are situations inherent to pregnancy and/or newborns, which by their mere presence increase the risk of contracting NEC.

Maternal factors are eclampsia; pre-eclampsia; multiple pregnancy; pre-gestational diabetes. Neonatal factors are bacterial colonization of the intestine (birth canal); prematurity; low birth weight (less than 1,500 g); heart malformations; and other surgical malformations [12]. Once the group of patients at risk has been established, prevention strategies can be developed, such as prolonging the period of careful observation of adaptation before starting enteral feeding on demand, among others.

The predisposing neonatal episodes are clinical episodes of stress to the NB, predisposing to IR, and mesenteric hypoperfusion. Maternal predisposing episodes are premature rupture of membranes; gestational diabetes; fetal suffering; placental abruption; and urgent cesarean section. Neonatal predisposing episodes are acute fetal distress; RN respiratory distress; perinatal hypoxia that requires resuscitation of the newborn; hypothermia; hypoglycemia; early enteral feeding despite the presence of risk factors; umbilical catheterization; prolonged neonatal surgery, etc. This sequence of pathophysiological events initiated by IR has clinical, laboratory, and radiological manifestations which are varied. But all manifestations are alterations of the intestinal wall, especially the presence of blood in the stool, which signifies ulceration or desquamation of the intestinal mucosa.

Clinical signs

The clinical signs of vomiting, abdominal distention, and macroscopic intestinal bleeding manifest from alteration of the intestinal wall. They are objective signs that do not depend on the interpretation of the observer since vomiting and blood are visible to the naked eye. By measuring the abdominal perimeter, the progress or decrease of distension can be recorded hour by hour (Fig. 1.).

Laboratory and cabinet testing

Altered laboratory data from blood tests, increased lactic acid, metabolic acidosis, procalcitonin, plasma endotoxin levels, and blood dyscrasias (thrombocytopenia, fibrinogen alteration, prothrombin time, prothrombin index, etc.), are objective from plasma analysis related to damage to the intestinal mucosa. In the stool, the data showing mucosal alteration are calprotectin and the guaiac test, which shows occult blood.

The radiological signs that are considered useful for diagnosis are the dilation of the intestinal loops (without air-fluid levels), the thickening of the walls of the intestine and interaseedema, which occur early (Fig. 2.), and finally, the characteristic intestinal pneumatosis (Fig. 3). Complete abdominal veiling and pneumoperitoneum are radiological signs of peritonitis.

By ordering these signs appropriately according to their appearance over the hours, we can identify simple, objective, and reproducible parameters that help to establish an early diagnosis of NEC disease. Following the suggestions of Gephart et al., Jaime Knell and the Vermont Oxford Network (VON) [14-16] established the diagnosis of NEC with the presence of a clinical sign, a laboratory finding, and a radiological one. As an alternative, the "two out of three" rule of these signs can be used to diagnose an established disease

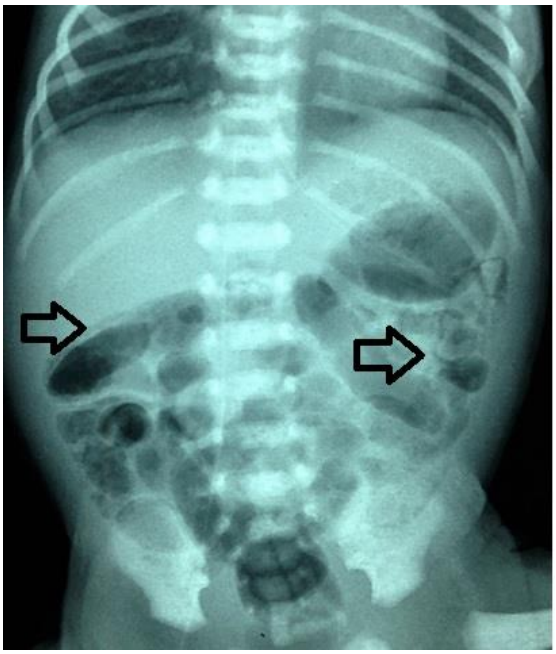

Fig. 3 The arrow indicates one of the areas compromised with intestinal pneumatosis (right colon and sigmoid).

before intestinal pneumatosis is established, especially when a history of blood in the stool of the newborn is demonstrated.

Conclusions

In conclusion, we could recover the "lost thread in the skein" according to the following:

1. Recognizing and ordering the risk factors of inducing IR in the perinatal period and the predisposing neonatal clinical episodes for IR, with which we could identify the newborns at risk of contracting the disease, regardless of whether they are premature or term born.

2. The parameters taken into consideration, clinical signs, laboratory data, and radiological signs are simple and objective since they do not depend on the interpretation of the observer. They are consistent and suggestive of being valid to establish the diagnosis of NEC in early stages of evolution.

Abbreviation

NEC: Necrotizing enterocolitis. NB: newborn. IR: immersion reflex.

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Authors' contributions

The author performed the conceptualization, data preservation, formal analysis, fund acquisition, research, methodology, project management, resources, software, supervision, validation, visualization, writing - original draft, writing: review and editing.

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Availability of data and materials

The data sets generated and / or analyzed during the current study are not publicly available due to the confidentiality of the participants, but are available through the corresponding author upon reasonable academic request.

Ethical statements

Protection of people

Does not apply to a narrative review.

Data confidentiality

The authors declare that they have followed the protocols of their work center on the publication of patient data without identification.

Publication consent

Does not apply to a narrative review.

Conflicts of interest

The author declare that they have no conflicts of interest.

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