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LITERATURE REVIEW

Neonatal Necrotizing Enterocolitis

by

H. TJANDRA

(Department of Child Health, Medical School University of Sam Ratulangi, Manado)

Abstract

Neonatal Necrotizing Enterocolitis (NEC) is a highly lethal disease of the newborn infant, which has aroused great interest in the past decades. It is characterized by ischemic necrosis of the intestinal wall, frequently leading to perforation and death. Unlike most neonatal emergencies, it is acquired and can be successfully treated without operation in most cases.

The etiology is still obscure and is considered to be multifactorial. Intestinal ischemia, infections, cow's milk, and hyperosmolar feeding are among the important factors associated with the pathogenesis of NEC in the newborn Many other factors are also related to the occurrence of this disease but some of them are still controversial.

The general opinion is that requiring a background of mucosal ischemia and damage; the presence of both intestinal bacteria and enteric feedings appear to be of significant etiologic factors.

The important pathologic lesion is the mucosal damage and necrosis involving mostly the ileum and colon except the duodenum. Perforations usually occur in the ileocecal region where the intestinal wall is extremely thin.

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Necrotizing enterocolitis in the newborn mostly affects the low-birth-weight infants, although its occurrence in full-terms has also been reported. Clinically, it is characterized by abdominal distension, hemato chezia, and pneumatosis intestinalis. Abdominal roentgenography is by far the most specific and sensitive test for confirming the diagnosis. In the attempt to make an early diagnosis it was suggested that an increased concentration of fecal reducing substances using the Clinitest method has an obvious merit in the detection of clinical manifestations in "at risk" babies.

In spite of a better treatment and management, the mortality remains considerably high. An early and aggressive therapy which demands an acute awareness of the significant symptom complexes, particularly in prematures, is of utmost important if the mortality is going to be improved. Medical treatment is the method of choice which includes nasogastric suction, intravenous fluid therapy, and systemic antibiotic for at least a 10-day period. With the improvement of medical treatment and management, there seems to be less and less patients requiring surgical intervention.

Many trials have been conducted in the prevention of either intestinal perforation or of the incidence of Neonatal Necrotizing Enterocolitis. All these await ongoing studies since definite conclusion still cannot be obtained.

Due to the relatively high incidence of low-birth-weight infants in developing countries, the possibility of Necrotizing Enterocolitis in the neonatal emergency cases has to be always taken in account.

Introduction

Neonatal Necrotizing Enterocolitis (NEC) is a highly lethal disease of the gastrointestinal tract in the newborn, primarily in low-birth-weight infant, and is characterized by ischemic necrosis of the bowel wall frequently leading to perforation and death (Mizrahi et al., 1965; Touloukian et al., 1967). It was Generisch (1891) who first reported on this entity, followed by Thelander in 1939 and Agesty et al. in 1943. Not until 1964 and 1965 was this clinical entity reported comprehensively by Berdon et al. and Mizrahi et al. respectively from the Babies Hospital, New York, followed by a significant surgical experience recorded for the first time by Touloukian et al. from the same institution in 1967.

This paper tries to present a brief review on this highly lethal yet salvageable disease of the newborn infant.

Etiology and pathogenesis

The etiology of Necrotizing Enterocolitis (NEC) in newborn infants is incompletely understood (Hakanson and Oh, 1977; Hutter et al., 1976), but that the etiology is multifactorial is obvious. Only low-birth-weight infants are mostly affected (Frantz et al., 1975), although its occurrence in full-terms has also been reported (Polin et al., 1976). Neonatal asphyxia is frequently suggested as a prime factor in the etiology of NEC (Hakanson and Oh, 1977). Many others have been hypothesized as possible factors of which some of them are still controversial.

Intestinal ischemia (Book et al., 1975), infections (Mizrahi et al., 1965), cow's milk (Barlow et al., 1974), hyperosmolar feedings (Book et al., 1975), and several other factors are considered to have a close relationship with the pathogenesis of NEC in newborns.

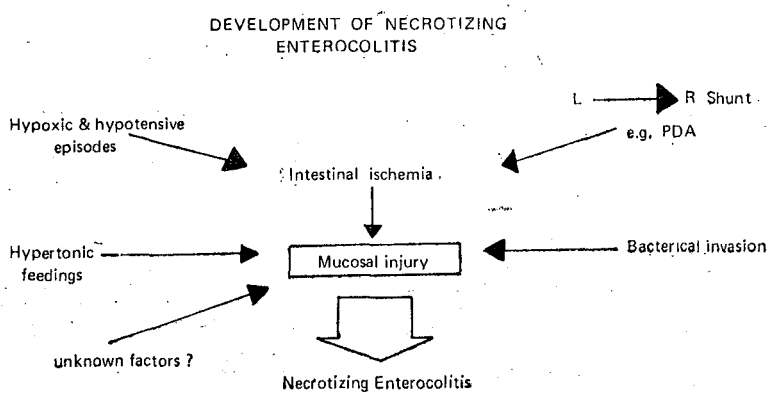
There are 3 essential components for the development of the disease (Santulli et al., 1975): injury to the intestinal mucosa, presence of bacteria, and the availability of a metabolic substrate, i.e. feedings (Engel et al., 1973; Frantz et al., 1974; Polin et al.,1976). Direct injury to the mucosa may be related to hyperosmolar feedings by alternating intestinal perfusion (Book et al., 1975). Indirect injury to the mucosa results from selective circulatory ischemia. This is the most acceptable theory of pathogenesis which is based on "the master switch of life" (Scholander, 1963), and which occurs as a physiologic and protective mechanism in diving mammals and birds. This was emphasized by Lloyd (1969) as an important etiology of gastrointestinal perforations of the newborn infant. The high incidence of infection found in NEC has been reported by many authors which is mostly caused by gram-negative microorganisms such as, Salmonella (Stein et al., 1972), Klebsiella (Hill et al., -974), and E. coli (Speer et al., 1976). These implicate enteric bacteria in the pathogenesis of the disease. The exclusion of

breast milk and substituting it with cow's milk have also been considered as important factors (Barlow et al., 1974). Macrophages in the breast milk have been assumed to be a protective component against NEC (Pitt et al., 1974). Barlow et al., (1974) were of the opinion that large amount of SIgA, IgG, active lymphocyte and specific antibodies in breast milk play a protective role. Mizrahi et al., (1965) pointed out that lysozyme deficiency of cow's milk formulas is responsible for the development of NEC in prematures fed cow's milk. A single case of the disease asssociated with milk intolerance has been reported (Aziz, 1973). Recently Powell (1976) also described in detail 2 infants with a syndrome indistinguishable clinically from NEC and provided carefully a documented evidence of an association between their illness and intolerance to whole protein (milk and soy) in the neonatal period. Due to the small number of cases, Book et al., (1976a) were unable to conclude whether a rapid-feeding rate played a role in the development of NEC.

Exchange transfusion remains a controversial factor in its relation to NEC (Corkery et al., 1968; Frantz et al., 1975; Roback et al., 1974). So is the relationship between low Apgar score, umbilical catheter, and the occurrence of NEC (Bell et al., 1971; Dudgeon et al., 1973; Hopkins et al., 1970). Two vascular components which are possibly associated with the development of NEC in small preterm infants are Patent Ductus Arteriosus (Kitterman, 1975) and hyperviscosity (Leake et al., 1975).

Other factors which once had also been suggested were, Schwartzman-type reaction (Hermam, 1965) and immunologic immaturity (Roback et al., 1974) etc.

Summarizing these, Frantz et al. (1975) stated that perhaps requiring a background of mucosal ischemia, the combined presence of intestinal bacteria and enteric feedings appeared to be of etiologic significance in the development of NEC. Below is a schematic diagram illustrating the possible pathogenesis of NEC (Adapted from Book et al., 1975):



Pathology

Early pathologic lesion is the mucosal damage and necrosis (Hopkins et al., 1970), involving all parts of the alimentary tract of which most common sites are the ileum and colon (Bell et al., 1971; Berdon et al., 1964; Santulli et al., 1967).

The diseased intestine is dilated and hemorrhagic, gray or necrotic (Dudgeon et al., 1973; Touloukian, 1976). The affected mucosa is covered by a pseudomembrane consisting of agglutinated inflamatory cells, fibrin, and necrotic epithelium (Berdon et al., 1964; Touloukian et al., 1967). There is a normal distribution of ganglion cells throughout the intestines (Berdon et al., 1964; Touloukian et al., 1967). Intramural gas (pneumatosis) in the form of gaseous strips or bubbles are present both submucosal and subserosal (Bell et al., 1973; Hopkins et al., 1970; Stevenson et al., 1971). The affected tissue is so friable that it may brick of and separate with handling (Stevenson et al., 1971). No evidence of vasculitis is seen (Bell et al., 1971; Stevenson et al., 1971). Primary microscopic findings are variable, ranging from submucosal hemorrhage, edema, and ulceration to vascular engorgement and thrombosis. Perforations are usually seen in the ileocecal region where the intestinal wall is extremely thin (Touloukian, 1976). The pathologic lesion is found either in premature babies or term infants (Polin et al., 1976).

Clinical manifestations

The incidence of this clinical entity ranges from 0.3 to 8% in various neonatal intensive care units (Bell et al., 1971; Dudgeon et al., 1973; Roback et al., 1974; Touloukian, 1976). The onset of the clinical signs and symptoms is mostly between the end and 7th day of life with a mean of day 4 to day 5 (Hopkins et al., 1970; Mizrahi et al., 1965; Touloukian et al., 1967). "At risk" babies are those associated with low-birth-weight (< 2000 gm) and gestational age of 34 weeks or less, and they will have other life threatening conditions such as Hyaline Membrane Disease, Congenital Heart Disease, sepsis (Roback et al., 1974), apneic spells, cyanosis (Santulli et al., 1975) and so on.

Clinically this is characterized by temperature instability, lethargy, irritability, prolonged gastric emptying, apnea, abdominal distension, ileus, followed by bile-stained non-projectile emesis and bloodstreaked stools (Berdon et al., 1964; Denes et al., 1970; Tan et al., 1972; Vollman et al., 1976).

The clinical diagnosis is confirmed by X-ray examination in over 98% of the cases (Stevenson et al., 1971). Abdominal roentgenography is by far the most specific and sensitive test for the presence of this condition (Bell et al., 1971). This was, however, denied by Richmand and Mikity (1975) who stated that radiographic appearance of NEC is nonspecific and may be seen in

other entities in the neonatal period which produces bowel necrosis, such as mesenteric arterial or venous occlusion or intestinal volvulus.

In order of decreasing frequency the radiographic features include : a. intestinal distension, b. intramural gas or pneumatosis intestinalis, c. free air in the peritoneum (pneumoperitoneum) and d. hepatic portal venous gas (Santulli et al., 1975; Touloukian et al., 1967).

Intestinal distension in the form of multiple, dilated loops of small bowel is most common, and although it may precedes pneumatosis intestinalis, it is not as specific or diagnostic sign (Santulli et al., 1975; Stevenson et al., 1971; Touloukian et al., 1967). Pneumatosis intestinalis is considered as the most common, frequent, and conspicuous radiographic finding (Hopkins et al., 1970; Stevenson et al., 1971) although not specific (Robinson et al., 1974), confirms the diagnosis of NEC (Vollman et al., 1976). Only it must be noted that there is no correlation between the extent of pneumatosis and the clinical severity or outcome of the disease (Bell et al., 1971; Frantz et al., 1975; Roback et al., 1974). Pneumatosis coli without small bowel pneumatosis has generally a far better response to medical management (Leonidas and Hall, 1976). Pneumoperitoneum varies from a smal volume seen only in the erect film to massive amounts of free air producing the "football sign" with "stitching of the football", represented by the falciform ligament outlined by air on either side of it (Berdon et al., 1964; Santulli et al., 1975). It is a late finding (Stevenson et al., 1971) and an indication for operation (Touloukian, 1976). Hepatic portal venous gas, a portal flow towards the liver which causes the gas to be seen as fine arborizing channels within the liver distributed well out to the periphery was first noted by Wolfe and Evans in 1955.

This is also a late finding (Stevenson et al., 1971), and is an ominous sign in infants with NEC, often associated with overwhelming septicemia and poor prognosis (Tan et al., 1972; Touloukian et al., 1967; Vollman et al., 1976); yet its presence is not always an indication of surgical intervention (Richmond and Mikity, 1975; Vollman et al., 1976).

In their study of 64 newborn infants with NEC, Polin et al., (1976) were of the opinion that even pathologically no difference exists between term infants and prematures; clinically it is somewhat different. In term infants no asphyxia at birth is found, in contrast to the prematures who are asphyxiated. Protracted diarrhea occurs exclusively in mature infants. Thrombocytopenia and leukopenia occur much more commonly in the premature infants, whereas leukocytosis occurs more frequently in term infants. The classic radiologic features are encountered less frequently in term infants than in premature ones.

Hutter et al., (1976), investigating 40 infants with severe NEC, concluded

that a low absolute granulocyte count is associated with a poor prognosis. Thrombocytopenia occurs commonly in babies with NEC (Touloukian, 1976) and is considered a significant problem in severe NEC, but may occur with or without evidence of fulminant intravascular coagulation (Hutter et al., 1976).

Diagnosis

The diagnosis of NEC may be made on the basis of symptoms in the first few days of life. Usually an infant of low-birth-weight, who has been doing well and taking feedings, begins to vomit or exhibits delayed emptying of the stomach (Mizrahi et al., 1965). This will be followed by abdominal distension, bloody stool, and pneumatosis intestinalis. These are usually seen only in fulminant diseases with extensive bowel necrosis (Bock et al., 1976a). If untreated, the infant deteriorates rapidly showing signs of sepsis, DIC and death (Touloukian, 1976). Early recognition is, therefore, vitally important if the outcome is going to be improved. Stevenson et al., (1971) strongly recommended abdominal radiographs for any infant who shows evidence of either a generalized systemic disease as manifested by temperature instability, increased apneic episodes, irritability or lethargy, or whose abdominal findings are distension, delayed gastric emptying, or blood in the stools. In the attempt to make an early diagnosis, Herbst (1975) showed that an increase in the concentration of reducing substances in the stool of a premature formula-fed baby, using the clinitest method, actually precedes the clinically recognizable signs of acute NEC. Using the same method, Book et al., (1976b) suggested that any formula-fed premature infants, demonstrating higher than 2-plus fecal reducing substances, deserve careful observation for signs and symptoms of NEC or other serious intestinal disorders. This test, routinely used in all "at risk" babies, has obvious merit in the detection and prevention of the clinical manifestations of NEC (Touloukian, 1976). Radiographic examination of the abdomen is then of utmost importance in establishing the diagnosis by identifying the most frequent, common, and conspicuous signs such as abdominal distension, pneumatosis intestinalis, hepatic portal venous gas, or pneumoperitoneum.

Only a few disease of the newborn infants mimics this condition, e.g. meconium ileus, intestinal stenosis, meconium plug syndrome, and Hirschprung's disease. These should be differentiated radiographically from the earliest signs of NEC which is a nonspecific intestinal dilatation. A careful history taking. physical examination, and a correct interpretation of the radiographic pictures are important in arriving at proper diagnosis.

Prognosis

Although the prognosis of NEC is serious once the disease is established, appears that the survival rate will be significantly improved by the institution

of early and aggressive therapy (Santulli et al., 1975). This demands an acute awareness of the significance of the symptom complex, particularly in the premature infants. In spite of improvement, the mortality remains considerably high, viz 30% - 70% (Behrman, 1973; Frantz et al., 1975). Early recognition and prompt treatment are essential for survival.

Treatment

The medical treatment includes continuous nasogastric suction or decompression, intravenous fluid therapy, systemic antibiotics, close attention to their acid-base and electrolyte balance, frequent physical examination, and roentgenologic studies every 4 - 6 hours to detect the presence of pneumoperitoneum (Frantz et al., 1975; Santulli et al., 1975; Touloukian, 1976). Enteric feeding is entirely discontinued. Intravenous alimentation has to be given until 10 days before oral feeding can be reinstituted. This is due to the fact that reinstitution of oral feeding prior to 10 days usually will lead to reappearance of clinical and radiographic signs of NEC (Frantz et al., 1975; Touloukian, 1976). This might be explained by the observations of Joshi et al., (1973) that epithelialization occurred as early as 3 days after the onset of NEC, but the formation of granulation tissue and fibroplastic proliferation were seen within an 8 or 9 day period.

The indications for surgical intervention are: intestinal perforation indicated by pneumoperitoneum, metabolic acidosis, and/or shock and DIC (Frantz et al.,1975), peritonitis, intestinal obstruction, and respiratory insufficiency (Dudgeon et al., 1973; Santulli et al., 1975). Hepatic portal venous gas, which was once considered an ominous roentgenographic sign and regarded as an indication for surgery, has been successfully treated medically by Vollman et al., (1976). Touloukian (1976) also stated that while previously thought to be a terminal finding it has been survived following aggressive medical treatment. It seems that a vigorous and continuous medical treatment and management for at least 10 days is necessary in NEC and can possibly minimize the risk of surgical procedures.

Operative survival equals and occasionally exceeds that of purely medical treatment (Touloukian, 1976). In his series, Touloukian (1976) at Yale-New Haven Hospital from July 1973 to October 1975, had a survival rate of 40% (4 out of 10) medically, and 50% (5 out of 10) surgically. The operative survival taken from more recent reports is even better; Wayne et al., (1975) had a 70% (21 out of 30) survival rate of their operative patients. This, according to Touloukian (1976), is a reflection of a better preoperative preparation, earlier recognition of irreversible signs, and the supportive post-operative care, including the use of parenteral nutrition. Frantz et al., (1975), however, in their series found 7 out of 16 (44%) of the medically and 12 out of 38 (31%) of

the surgically managed patients who had survived. Notwithstanding the difference of the results of treatment, either surgically or medically, for the time being, a close cooperation of both the Surgical and Pediatric departments for us is a condition sine qua non in lowering the mortality rate of NEC.

Prevention

Low molecular weight dextran has proven effective in the prevention of intestinal perforation of babies with NEC. In the initial report by Krasna et al., (1973), 4 out of 8 babies receiving the dextran treatment did not require operation, while all of the patients not receiving dextran did. Another effort in the prevention of bowel perforation in NEC has been done by Bell et al., (1973) by adding topical antibiotics through nasogastric tube besides the routine treatment. None of the 14 babies developed free intestinal perforation in this trial. Encouraged by this, Egan et al., (1976) conducted a prospective trial of alimentary Kanamycin (15 mg/kg.b.w./day) in very low-birth-weight infants to determine if prophylactic therapy would lower the incidence of the disease. They concluded that Kanamycin did lower the incidence of NEC, but doubted that it would absolutely prevent it. This has been negatively commented by Nelson (1976). The use of breast milk in this case still awaits results of ongoing studies (Touloukian, 1976). Further investigations on this aspect is justified.

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