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Case Report

Risk Factors in Recurrent Necrotizing Enterocolitis – A Case Report

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Abstract

Necrotizing enterocolitis (NEC) is one of the common gastrointestinal disease in preterm neonates associated with high morbidity and mortality. The incidence of NEC is related to gestational age and birth weight. Despite of extensive research, the etiology and mechanism of NEC is not completely understanding and therefore high incidence of NEC in preterm infant is currently an unsolved problem. The recurrent rate of NEC is only 4 - 6% in literature. We reported a case of a 29+2 week preterm infant, with very low birth weight (1380g). He developed four episodes of recurrent NEC. He started from mild form with gastric residuals, having ended in bowel obstruction in the last episode. We analyze the risk factors that was responsible for recurrent NEC. Early identification and intervention may reduce the incidence and morbidity of NEC.

Keyword: *Necrotizing Enterocolitis; Recurrence*

Introduction

Necrotizing enterocolitis (NEC) is a gastrointestinal emergency in both preterm and term infants, manifested by inflammation, ischemic and necrosis of the intestinal mucosa. After first described by Mizrahi., *et al*. [1] in 1965, Bell., *et al*. [2] classified NEC into three stages according to the clinical presentation and radiographic appearance. Later, new criteria, called modified Bell's criteria proposed by Walsh and Kliegmena combined laboratory finding in originate criteria, providing the complete diagnosis and therapy [3].

The incidence of NEC is inversely proportional to gestational age (GA) and birth weight (BW), occurs in 1 to 3 per 1000 live births and dominate around 90% in preterm infants [4]. Incidence in very low birth weight infants (BW less than 1500g) are approximately 7%, with a mortality rate up to 15 - 30% [5].

The pathogenesis of NEC has not yet been much explored, but most likely multifactorial causes: prematurity, bacterial colonization of the preterm gut and formula feeding [6].

Diagnosis of NEC depends on clinical presentation, radiographic and laboratory results. The most common gastrointestinal symptom was feeding intolerance, includes emesis or increased gastric residuals (defined as gastric stasis larger than 2 ml/kg or > 50% of previous feeding volume) [7,8]. Other nonspecific symptoms include abdominal distension, occult or gross blood in stool, absent bowel sound, abdominal wall discoloration and sign of sepsis (tachycardia or bradycardia, hypotension). Radiographic finding consistent with NEC are dilated intestinal loops, pneumatosis intestinalis with portal venous gas and pneumoperitoneum. Laboratory finding assist in diagnosis of NEC refer to thrombocytopenia, neutropenia, hyponatremia and metabolic acidosis.

Management of NEC depends upon the severity of disease, as classified by the Bell criteria, with medical management with or without surgical intervention.

Medical management is a crucial treatment, which includes fasting, gastric decompression, intravenous antimicrobial therapy, fluid and nutrition replacement, suitable for Bell stage I and II NEC. Whereas surgical intervention is need for advanced NEC complicate with intestinal perforation and presented pneumoperitoneum.

Despites numerous studies focus on prevention and management of NEC in preterm are discussed in literature in past decades. NEC is the most common cause of gastrointestinal related morbidity and mortality in neonatal intensive care units. The prevention is very important and the first question that arises concerns earlier identification of risk factor of NEC. We share a case of recurrent NEC in a VLBW preterm infant, who developed NEC with perforation.

Case Report

We described a preterm male infant, monochorionic diamniotic (MCDA) twin 2, with gestational age of 29 and 2/7 weeks that developed 4 times NEC complicated with bowel perforation.

The pregnancy was complex by preterm labor since 26 and 3/7 weeks of gestational age. Maternal antibiotics and betamethasone were given prior to delivery. An emergent cesarean section was performed due to one of fetus cease heartbeat. Two infants were delivered, with one stillbirth. Another male infant, weighing 1380g, was floppy with no spontaneous breathing. Apgar scores of 4, 8, 10 were appointed at 1, 5 ,10 minutes of life respectively. He was admitted to NICU for further mechanical ventilation and supportive care because of prematurity, very low birth weight (VLBW) and prenatal asphyxia. Blood analysis revealed severe anemia, with hemoglobin 3.7g/L. Chest X-ray (Figure1) showed diffuse ground lungs which represented hyaline membrane disease (HMD). He was received 2 doses of curosurf for HMD and RBC transfusion in 15 ml/kg was given. Control Hb increased to 11 g/L. He developed hypotension and needed inotropes (dopamine) support for 5 days since D(day)2. Prophylactic antibiotics of penicillin and netilmycin was given for 7 days and discontinued after a negative blood culture. Enteral feeding of preterm formula was given in small volume (15 ml/kg/day) since D2 and gradually increased to large volume (127 ml/kg/day) on D13. He had occasionally gastric stasis within 50 - 60 ml. On D14 he vomited several times after each feeding, passed stool mixed some bloody liquid. Blood analysis revealed hyponatremia (Na 125 mmol/L). Abdominal X-ray (Figure 2) indicated disseminated pneumatosis intestinalis, consistent diagnosis of NEC (1st time NEC). Fasting, fluid replacement and empirical antibiotics of penicillin, metronidazole was given. On D18, scleroderma was found over buttock, lower limbs, scrotum, and fluconazole was added. Blood analysis showed anemia (Hb 9.4 g/L), thrombocytopenia (35,000) and increased CRP (19.4mg/dL), then RBC transfusion was given. TPN support was given since D24. Totally fasting for 17 days due to persistent hematochezia, which stopped after 1:10000 Adrenaline 1 ml and water inserted under gastric tube, frozen plasma infusion and vitamin K injection.

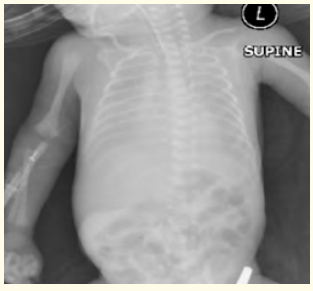

Figure 1: *Diffuse ground lungs which represented hyaline membrane disease (HMD).*

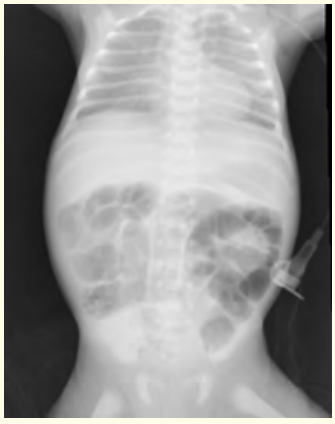

Figure 2: *Disseminated pneumatics intestinalis.*

On D34, two days after normal brownish stool and resume small volume of diet. Positive blood culture of staphylococcus hemolytic was noted. Further blood analysis found leukocytopenia (WBC 2.4 x 10e9/L), and vancomycin plus meropenam were given. On D38, patient passed green stool with small blood clot mix stool 1 time (2nd time of NEC). Fasting was given for 3 days.

On D50, patient vomited and passed bloody stool again. Control blood test showed leukocytosis (WBC 23.9 x 10e0/L) and anemia (Hb 9.0g/L). Abdominal X-ray (Figure 3) revealed bowel loop dilation, left decubitus view: fluid air level. In this 3rd time of NEC, totally fasting was during 7 days, and TPN plus meropenam were given.

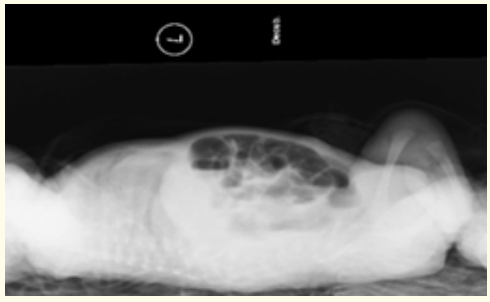

Figure 3: *Bowel loop dilation, fluid air level.*

On D60, patient developed significant abdominal distension and cease bowel movement. Abdominal X-ray (Figure 4) showed significant bowel dilation, with air fluid level, consistent of gastrointestinal obstruction. Since there was not improved after 3 days of conservative management, laparotomy exploratory was performed. We found multiple intestinal adhesive with banding on root of mesenteric region with atresia section noted on terminal ileum. A small perforation found in small bowel. Lysis of intestinal adhesion plus resection terminal ileum with cecum and appendix. Ileuo-colostomy was performed.

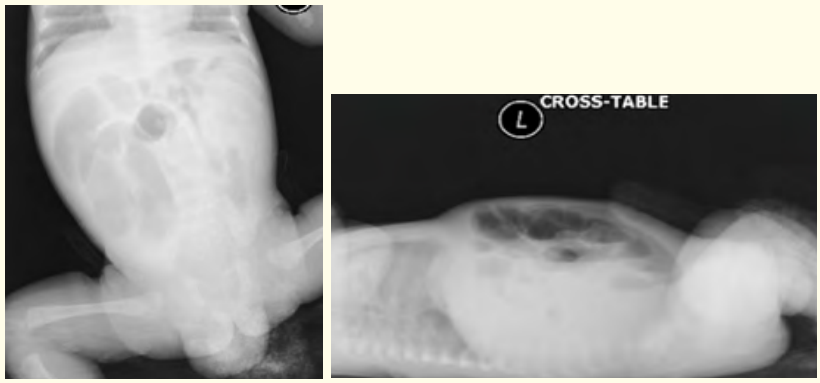

Figure 4: *Significant bowel loop dilation, fix bowel loop, with air fluid level.*

The pathology reported that the overall appearance of a segment of intestine (3.4 cm) showed membranous atresia with intact bowel wall and mesentery. There was an area of narrowing of intestine, measuring 0.8 cm in length at the mid portion. Microscopically there showed luminal narrowing with granulation tissue and fibrosis, associated with recognizable intestinal wall with muscular layer and granulation tissue with fibrosis at the mesentery. Both proximal and distal mucosa was viable. Rest of mucosa showed foci of ulceration, presence of goblet cells, collecting foamy histocytes containing brownish pigments, acute inflammatory process and granulation tissue with sign of congestion.

Patient was resumed formula feeding 4 days post operation, and tolerated feeding. He was discharged on D88, 25 days after operation, weighting 2.66 kg.

Discussion

We presented a case of critical NEC of a preterm infant in VLBW. There were totally 4 times recurrent episodes of NEC. Patient improved in the first 3 episodes under medical management. Unfortunately, in the last NEC complicated with intestinal obstruction and perforation required surgical intervention.

There were several risk factors inducing NEC in our case, described as below:

Preterm birth

Prematurity is the most crucial risk factor for NEC. Majority of infant with NEC are born prematurity. Simply stated, highest risk of NEC occurs in lowest gestational age [9]. Incidence of NEC in term infants are approximately 13 %. Pathogenesis of NEC in term infants typically have pre-existing disease such as congenital heart disease, sepsis, seizures, etc. [10,11]. Besides, onset time of NEC differs inversely from gestational age. NEC occur within the first week of life in term infants, whereas between 2 and 3 weeks of life in preterm infants [12]. In fact, the intestinal epithelial acts on an important barrier in term infant. Premature infant gut displays impair of intestinal barrier function, decrease intestinal motility and urge of gut inflammation [13]. While compared to the mature intestine, the immature one is more probable to stimulate cytokine-mediated inflammatory responses by interleukin-8, which increases neutrophil chemotaxis and inflammation that can lead to tissue injury and NEC [13].

Hypoxia and shock

In our index case, the patient developed perinatal asphyxia after delivery, required resuscitation and immediate mechanical ventilation (MV). Besides, hyaline membrane disease with respiratory distress arose on D1, which needed curosurf replacement. Various studies claimed that both resuscitation and MV related to unstable hemodynamic are risks of NEC. Hypoxia triggers production of inflammatory mediator and initiation of inflammatory cascade which result in intestinal ischemia-reperfusion injury [14]. Moreover, Gregory [15] declared that incidence of NEC increased 13 times in infants who received mechanical ventilation, especially in birth weight of 500 - 1500g and less than 28 gestational age. Our case, the newborn weighted 1380g.

Anemia

Anemia is a predisposing risk factor of NEC. In our case, severe anemia (Hb 3.9g/L) occurred as a consequence of twin twin transfusion syndrome (TTTS). Anemia related to TTTS lead to poor perfusion of GI tract, especially in the donor infant [16]. Therefore, an array of hypoxia metabolic process was launched and caused injury of preterm gut endothelium and apoptosis of mucosa [17] Blood transfusion as a risk of NEC is controversial. Mohamed., *et al*. [18] indicated that packed red blood cell transfusion associated with NEC, with incidence of 7.5%, especially within 48hours after transfusion. However, in a recent prospective study, Patel., *et al*. [19] argue that there was no relationship of blood transfusion and NEC, but severe anemia remains a potential risk factor for NEC.

Feeding

Since it was a preterm baby, judicious advancement of enteral feeding: preterm formula (between 15 and 25 mL/kg/day) was given in our case since D2. Patient started gastric stasis (> 50% of previous feeding) since D4. Cobb., *et al.* [7] suggested gastric residual volume > 3.5 ml or 33 % of single meal probably increased risk of NEC. Therefore, in such a feeding intolerance may represent an early signal of NEC and it was until D 14 that patient developed NEC presented with hematochezia. In the past few decades, numerous articles discuss about the optimal timing, speed and substance of infant feeding focus on decreasing NEC. Early (defined as beyond 4 days after birth) or delay feeding (defined as less than 5 - 7 days after birth) was compared in literature in decrease risk of NEC, it is still controversial about the optimal timing of initiation of feeding. A systematic review by Morgan., *et al*. [20] published in Cochrane database announced that there is no difference in risk of NEC in VLBW infants of low volume feeding (15 – 24 ml/kg/d) and fast volume feeding (30 - 40 ml/kg). Human breast feeding, contains plenty of benefit bioactive factors, such as L-arginine, lactoferrin, platelet- activating factor acetylhydrolase, etc. is widely proved to prevent NEC [21].

In our case, patient developed bowel obstruction and perforation. Pneumoperitoneum do not present in abdominal X-ray. On the other hand, a small hole was found during operation. Actually, bowel perforation related to NEC is the fetal cause of preterm infants, especially in who is concurrent with multiple risk factors, such as lower birth weight, apnea and sepsis which presented in our case [22]. For early diagnosis of bowel perforation, any sudden onset of tachycardia and shock symptoms may imply perforation and further investigation by the clinician must be performed. Besides, Linder., *et al*. [23] described abdominal distension is a high-risk factor for bowel perforation in NEC. Except pneumoperitoneum finding in abdominal X-ray, any fixed intestinal loop manifestation may require surgical intervention [22,24].

Pathological result in our case revealed stricture of the small bowel secondary to recurrent NEC. It is a rare condition because mostly stricture occur in colon (80% of case) post NEC [25]. Heida., *et al*. reported that incidence of clinical relevant post-NEC strictures was 19%, with a higher rate (24%) in NEC cases who under surgical intervention [26]. It was almost 5-7weeks in apparent manifestation of stricture after onset of NEC [27]. Contrast enema is suggested in any suspicious case.

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