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Inflammatory Markers in the Diagnosis of Neonatal Necrotizing Enterocolitis

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Abstract: As a serious gastrointestinal disease in newborns, neonatal necrotizing enterocolitis (NEC) is characterized by an acute onset, rapid progression and high mortality. The pathogenesis of NEC is complex, which makes diagnosis difficult. The diagnostic gold standard of NEC occurs via intestinal biopsy, but this is not feasible for practical clinical applications. Therefore, the diagnosis of NEC at this stage mainly depends on clinical symptoms and abdominal X-ray imaging. However, the clinical symptoms of infants with early NEC are not specific and the characteristic manifestations seen on imaging often only appear during a critical state of NEC, which easily leads to misdiagnosis or the delay of treatment. Thus, finding a reliable diagnostic method to achieve early diagnosis and treatment is necessary to improve prognosis. As a simple and feasible new diagnostic method in the clinic, inflammatory markers have broad application prospects. In this paper, the common inflammatory markers for early diagnosis of NEC are reviewed from the aspects of the molecular mechanism, research status, and feasibility of the clinical application, including serum amyloid A, C-reactive protein, procalcitonin, fecal calprotectin, intestinal fatty acid binding protein, and cytosolic β-glucosidase. Studies have shown that inflammatory markers possess clinical potential for the early diagnosis of NEC, showing more advantages than traditional imaging methods. However, at present, the research is still limited to small sample and single-center research studies, and evidence from large sample sizes, multi-center studies, and multi-inflammatory markers will be needed to support by additional studies in the future.

Keywords: Neonatal Necrotizing Enterocolitis, Inflammatory Markers, Early Diagnosis, Literature Review

1. Introduction

Neonatal necrotizing enterocolitis (NEC) is an acute gastrointestinal disease which has seriously threaten the life and health of newborns. Although more than 50 years have passed since Person first reported it, the etiology and pathogenesis of the disease are still not fully understood. At present, NEC is considered to be related to many factors, such as premature delivery, improper feeding, abnormal bacterial colonization, infection, genetic susceptibility, and medical behavior [1]. Infections and intestinal inflammation are key factors in NEC [2]. Infection leads to intestinal mucosal barrier function impairment, leading to direct bacterial activity through lipopolysaccharides. Intestinal inflammation will mediate inflammatory reactions and produce cell-activating factors, causing or accelerating the occurrence of NEC.

With advances in technology and medicine, the survival rate of newborns has improved, especially in premature and very low birth weight infants (weight<1500 grams), The incidence of NEC is 0.3-12% and has shown an upward trend [3]. The incidence of NEC in very low birth weight infants is 4.5–8.7%, the mortality rate is 20–30%, and the mortality rate of extremely low birth weight infants (weight<1000 grams) is as high as 30–50.9% [4-6]. Early clinical manifestations of NEC are nonspecific. Full-term infants mainly show gastrointestinal symptoms such as vomiting and abdominal distension; some have bloody stools. Premature infants with an unstable body temperature, apnea, and bradycardia are more likely to show systemic symptoms and feeding intolerance. The hidden characteristics of the onset of NEC make it difficult to distinguish from gastrointestinal malformations, such as intestinal malrotation and neonatal sepsis. Simultaneously, NEC progresses rapidly, and the

mortality rate of stage III NEC is extremely high. Even if the child survives, there may be complications such as short bowel syndrome, intestinal stenosis, growth retardation, and neurodevelopmental retardation in later stages, seriously affecting long-term quality of life [7]. Therefore, it is important to diagnose NEC in its early stages to improve the survival rate of patients. Previously, NEC diagnosis primarily relied on clinical manifestations and abdominal radiographic examinations. However, because of the atypical early symptoms of NEC, it is easy to miss a diagnosis. Moreover, it is necessary to develop reliable methods for early diagnosis and treatment. Inflammatory markers are simple and easy to evaluate, showing promise as a new diagnostic method.

In recent years, many researchers focus on the inflammatory markers of NEC. The most investigated route is finding inflammatory markers in the blood or body fluids to achieve early diagnosis. Herein, inflammatory markers for the early diagnosis of NEC, including serum amyloid A (SAA), C-reactive protein (CRP), procalcitonin (PCT), fecal calprotectin (FC), intestinal fatty acid binding protein (I-FABP), and cytosolic β-glucosidase (CBG), are explored.

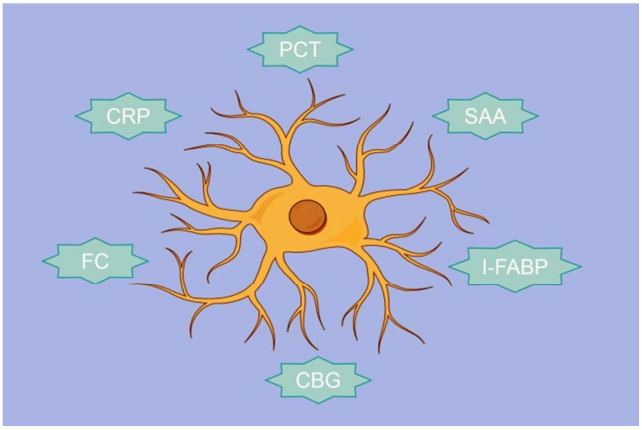

Figure 1. *Inflammatory Markers in the Diagnosis of NEC.*

2. Inflammatory Markers

2.1. Serum Amyloid A

As an acute-phase protein, SAA is produced by liver cells which stimulated by inflammatory factors, it also can originate from inflammatory tissues outside the liver [8]. The SAA levels can rise rapidly in 4–6 hours after infection and increase to 1,000 times the normal level in 8–24 hours. Because of its rapid increase, SAA can be used to determine whether infectious diseases occur in newborns at an early stage. Previous studies have shown that SAA participates in various organ inflammation and cancer reactions and has high clinical application value in diagnosing chronic obstructive pulmonary disease, rheumatoid arthritis, tumors, and other diseases [9-11]. In addition, SAA can also be used as an important reference in pediatric infectious diseases [12].

Liu et al [13] evaluated SAA, CRP, and SIRT1 in 100 infants with NEC and 100 healthy newborns. The diagnostic value of each index for NEC was analyzed using the receiver operating characteristic (ROC) curve, which showed that SAA level in the patients with NEC was higher than healthy participants. Additionally, the SAA level positively correlated with the modified Bell staging. The area under the curve (AUC) of SAA for NEC diagnosis was 0.822, and the sensitivity was 75.2%, the specificity was 69.4%. Further research showed that the sensitivity of SAA combined with CRP and SIRT1 in diagnosing NEC reached 94.3%, suggesting that the combination of CRP and SAA has a high diagnostic value for NEC. Zhai et al [14] divided 90 newborns into stage III/II, stage I, and non-NEC groups according to the modified Bell staging method and measured SAA levels in each group at different time points. The results showed that the SAA level gradually increases with NEC severity, and SAA has good sensitivity and specificity. In summary, SAA has a good clinical application value in diagnosing early NEC.

2.2. C-Reactive Protein

As one of the most widely used inflammatory indicators in a clinical setting, CRP is an acute-phase reaction protein synthesized by liver cells stimulated by cytokines. The CRP levels increase sharply when the body is infected and experiences trauma [15]. Changes in CRP levels are not influenced by physiological activities, chemotherapy, radiotherapy, hormone therapy, or other factors, and its rising level can reflect the scope and severity of inflammatory infections to some extent, therefore, some scholars believe that the continually high CRP levels can be used as a reliable indicator of intestinal infection [16].

Li et al [16] included 60 patients with NEC and 40 healthy newborns in a retrospective study and confirmed that CRP increased in the early stages of NEC, and the optimal critical value for the diagnosis of NEC was 5.836 mg/L. At the same time, the study recorded the number of deaths in the NEC group 60 days after birth. The results showed that the sensitivity and specificity of CRP in predicting the death of patients with neonatal NEC 60 days after birth were 61.5% and 96.2%, respectively, indicating that CRP can also be used as a prognostic indicator. Wen et al [17] measured CRP levels in 35 mild cases (NEC I and NEC IIa stages) and 23 severe cases (NEC IIb and NEC III stages) by immunoturbidimetry according to the Bell classification. The results showed that the CRP levels in severe cases were higher than those in mild cases at all time points. Spearman's correlation analysis showed that NEC classification was positively correlated with CRP level ($P < 0.05$). Therefore, CRP has good prospects for diagnosing and discriminating NEC severity. However, CRP is widely distributed in the human body and is sensitive to infection; therefore, it is easy to misdiagnose NEC if CRP is used as a single indicator [18]. Combining CRP with other indicators will greatly improve the clinical diagnosis of NEC [14].

2.3. Procalcitonin

PCT is a precursor of calcitonin which is considered a monitoring index for bacterial infections. Under normal

circumstances, the plasma concentration of PCT is lower than 0.1 ng/mL. However, the concentration of PCT in the blood will increase rapidly when bacteria enter the human body [19]. In severe infection, it can rise 5,000 times compared with the physiological state [20]. The PCT level in newborns can temporarily increase physiologically after birth and then return to normal quickly, while the serum PCT in infants with NEC remains high.

Xiao et al [21] compared PCT levels in the peripheral blood of 32 patients with NEC and 106 healthy newborns at different time, and found that the level of PCT in the patients with NEC was significantly higher than healthy newborns. Logistic regression analysis showed that increased PCT levels were associated with the occurrence of NEC. Jiang et al [22] found that PCT is a good indicator for NEC diagnosis, and its optimal critical value is > 0.5 ug/L. The ROC curve showed that the specificity of PCT was 69.14%, the sensitivity was 89.32%, and the AUC value was 0.856, indicating that PCT has good sensitivity for diagnosing NEC. In another study that included 47 infants with NEC and 45 premature infants without NEC, the results showed that the level of PC in infants with NEC was higher than those in the premature group without NEC [23]. Qian et al [24] detected the serum PCT levels of 90 infants with NEC and 80 healthy newborns using enzyme-linked immunosorbent assay (ELISA) and obtained similar results. In addition, the ROC curve analysis showed that the AUC of PCT combined with Platelet/Lymphocyte Ratio (PLR) and SAA for diagnosing NEC was 0.856, which was significantly greater than that of PCT alone (0.798).

Therefore, PCT has good potential for the early diagnosis of NEC, but its specificity is poor. Combined with other indicators, however, the diagnostic specificity can be improved.

2.4. Fecal Calprotectin

FC is a calcium-zinc-binding protein which is a member of S100 protein famil, derived from neutrophils and macrophages, and is one of the markers of acute inflammatory cell activation [25]. The level of FC in feces is six times that of peripheral blood [25]; therefore, it can be detected in the feces to reflect intestinal inflammation. FC is highly stable in the external and intestinal environments and is unaffected by microorganisms, intestinal digestive enzymes, or other factors, the stable characteristics of FC make it the good biological indicator for monitoring intestinal inflammatory activity [26]. Furthermore, it is convenient to obtain samples and has the advantages of non-invasiveness, repeated detection, and short detection time. Some neonatal researchers believe FC is a valuable marker for diagnosing NEC [27, 28].

Li et al [29] divided 84 premature infants with intestinal infection into NEC and non-NEC inflammatory groups and created a blank control with 50 premature infants without intestinal infection. After detecting the FC levels of infants in each group, it was found that the FC level of infants with intestinal infection was significantly higher than that of the normal premature infant group. The FC level of infants in the NEC group was higher than that of the infants in the other groups. Hu et al [30] divided 62 pairs of newborn cases into NEC and control groups and divided infants with NEC into stages using an improved Bell staging standard. The FC levels of the participants were measured by collecting fresh stool samples on the second day after admission. The results not only suggested that the FC level of infants in the NEC group was higher than that in the non-NEC group but also gradually increased with the aggravation of NEC. Xie et al [31] found through a meta-analysis that FC has high specificity and sensitivity in diagnosing neonatal NEC, which is helpful for its early diagnosis.

However, there are some inconsistent results by previous researches about the value of FC in the early diagnosis of NEC [32]. Owing to the wide range of FC concentrations in infants 0–6 months, there are significant differences among individuals. Currently, there is no uniform critical value of FC in diagnosing NEC [33]. After monitoring the level of feces in 100 high-risk newborns, Van et al [32] found no difference in FC concentrations between NEC and control infants from birth to the first suspicion of NEC. Van suggested that FC is not suitable for early diagnosis of NEC in high-risk newborns. Therefore, multicenter and large-sample clinical studies are needed to determine the application value of FC in the early diagnosis of NEC.

2.5. Intestinal Fatty Acid Binding Protein

I-FABP is a low molecular weight water-soluble protein with good organ specificity that only exists in the cytoplasm of ileal mucosal villous epithelial cells, easily damaged by ischemia and hypoxia [34]. Under normal physiological conditions, the serum concentration of I-FABP is extremely low. However, when intestinal mucosal villi are damaged, it can cause an increase in plasma I-FABP levels [35]. The increased level of I-FABP is proportional to the length of intestinal lesions and the degree of inflammation [36]. Because I-FABP has strong organ specificity, stable molecular structure, and is easily stored at room temperature, I-FABP levels can be detected in blood and urine by ELISA; therefore, it can be used as a biomarker for the early prediction of intestinal mucosal damage.

Du et al [37] collected blood samples from 111 fasted infants within 24 hours after NEC diagnosis and from 110 healthy newborns simultaneously. Serum I-FABP levels were measured by ELISA. The results showed that I-FABP levels in infants with NEC increased significantly and showed a gradual upward trend with the progression of the illness. Lu et al [38] also suggested that I-FABP levels in the NEC group were significantly higher than those in the control group, and the level of I-FABP level in infants with Bell stage III was higher than stage I–II. After treatment, the serum I-FABP level in 16 infants with poor prognosis was higher than that in infants with good prognosis, suggesting that I-FABP can assist in diagnosis and be used as a reference index for poor prognosis in NEC [38]. Based on the ROC curve, Lin et al [39] pointed out that the sensitivity of I-FABP in diagnosing NEC was 98%, and the specificity was 88%, and that the specificity significantly increased after combining I-FABP with Platelet

(PLT). Thus, I-FABPs are valuable inflammatory markers for the early diagnosis of NEC.

2.6. Cytosolic β-Glucosidase

CBG is a cellulase that is mainly distributed in intestinal epithelial cells. Some scholars believe that the change of β-glucosidase concentration occurs sooner than that of intestinal histology, an important biochemical index of intestinal injury [40]. CBG has been increasingly included in studies of NEC biological indicators in recent years.

Yan [41] used ELISA to detect serum CBG in 47 patients within 24 hours of entering the group. The results showed that the level of CBG in the patients with NEC was significantly higher than newborns without NEC and gradually increased with NEC progression. The ROC curve showed that the sensitivity and specificity of CBG in diagnosing NEC were satisfactory at 73% and 81%, respectively. According to radiography and clinical symptoms, 63 patients were divided into NEC and control groups. The results showed that CBG was highly expressed in the serum of infants with NEC and was positively correlated with NEC severity [40]. These results are consistent with those of previous studies [42]. In addition, urine CBG has a reference value for NEC diagnosis [43]. A retrospective study by Du et al [37] found that the CBG level in patients with NEC increased significantly, providing a reference for the early diagnosis of NEC, and the combination of I-FABP and CBG can improve the application value of early diagnosis. Therefore, serum or urine CBG levels can be used as a sensitive reference index for the early diagnosis of NEC in infants, and the diagnostic rate is higher when combined with other indicators.

3. Discussion

NEC is a serious intestinal necrosis disease caused by multiple factors and is one of the leading causes of neonatal death. At present, the diagnosis and staging of NEC primarily depend on clinical manifestations and abdominal radiographs. However, since the clinical symptoms of infants with early NEC are not specific, it is difficult to distinguish them from other digestive diseases; thus, NEC is easily misdiagnosed. Moreover, NEC progresses rapidly, the characteristic imaging manifestations often only appear during the critical state, and the interpretation of radiographic reports is often delayed. Therefore, the early diagnosis of NEC remains challenging.

In recent years, with an increasing number of scholars studying the diagnostic methods of NEC, biological markers have shown more advantages than traditional imaging modalities, such as lower cost, more straightforward and convenient procedures, more objective results, and no radioactive exposure, thereby having better application prospects. At present, research on NEC diagnostic markers is limited by small sample sizes, single-center studies, and other factors, and the results may be inaccurate. A large sample size, multicenter research, new markers, and joint detection of multiple markers will be the focus of future research efforts.

4. Conclusion

Inflammatory markers are a simple and feasible new diagnostic method that has clinical potential for the early diagnosis of NEC, and it shows more advantages than traditional imaging methods. However, the research is still limited to small sample sizes and single-center research studies. The clinical popularization of inflammatory markers needs more evidence from large sample sizes, multi-center studies, and multi-inflammatory markers to support this diagnostic method in the future.

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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