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ASSOCIATION OF INTERLEUKIN-6 AND INTERLEUKIN-11 WITH NEONATAL SEPSIS

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ABSTRACT : Sepsis or septicemia are severe bloodstream infections that can quickly become life-threatening. Sepsis is most often caused by bacterial infection and it is one of the major causes of mortality and morbidity in newborns (< 1 month).The aim of this study is to investigate the role of interleukin-6 (IL-6) and interleukin-11 (IL-11). The neonates ranged in age from 1 - 30 days, and blood samples were obtained to determine the levels of Interleukins IL-6 and IL-11.The findings of this study showed that (72%) of newborns have early onset sepsis (infected within the first seven days of their lives), while the remaining (28.3 %) have late onset sepsis (infected during 7-30 days of their life). Bacterial isolation was performed on the samples collected. Bacterial culture was positive in (60%) patients versus (40%) patients revealed a negative bacterial culture. The level of Interleukins was quantified using the adsorption test for immune antibodies binds to the enzyme (Sandwich ELISA test). The Interleukin levels showed that a significant increase in the level of interleukin-6 (IL-6) and interleukin-11 (IL-11) for all patients compared with a control group. The results showed that IL-6 and IL-11 can be a reliable marker for predicting neonatal sepsis and can be used as a good guide for early detection of sepsis in neonatal care units. The findings of this study revealed that IL-11 plays a protective role in sepsis patients with thrombocytopenia.

Key words : Interleukin-6 (IL-6), Interleukin-11(IL-11), bacteria, neonatal sepsis.

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INTRODUCTION

Neonatal septicemia is a more important syndrome of infections with bacterial at early stage of infant's life (Russell *et al*, 2015). Worldwide, the one of the largest causes of morbidity and mortality in infants is neonatal septicemia was classified as early onset sepsis (EOS) that occurs at age through one to seven days or late onset sepsis (LOS) that occurs at age through eight to twenty eight days (Jain *et al*,2003 and Edwards *et al*, 2006). The spectrum of infecting organisms has evolved over the last two decades from a predominance of G-bacteria to Gram positive bacteria. Most community-acquired infections are due to *Streptococcus* spp., *Escherichia coli*, other Enterobacteriaceae and non-ferment Gram-negative bacteria like *Pseudomonas and Acinetobacter* spp (Ramphal *et al*, 2004). It was reported that *Strep. agalactiae* (Group B *Streptococcus*) considers the main cause of meningitis and neonatal sepsis. Many clinical isolates of pathogenic bacterial species, including *Mycobacterium, tuberculosis, Enterococcuss faeceium*, *Staph. aureus*, *Pseudomonas aeruginosa*, *Kleibsiella pneumoniae*, *Neiseria gonorrhoae*, *Acinetobacter baumanii*, *Enterobacter*, *Salmonella* and *Shigella* spp. are resistant bacteria for many antibiotics. The problem remains out of control (Nathan *et al*, 2014). Many clinical diseases, includes upper respiratory tract; infection of urinary tract, cholecystitis, pneumonia, thrombophlebitis, wound infection; meningitis, osteomyelitis can led to bacteremia, sepsis and septic shock, that may result from the bacteria entering the blood stream (Jung *et al*, 2012). Cytokines define as proteins secreted (small polypeptides) by variety according to type of tissue cells, most commonly of the immunity system, that have functions of pleiotropic at the local tissue or sometimes at the systemic level. Different cell types' activation, growth and differentiation are all regulated by them. They work by binding to cytokine receptors on cell membranes, as well as plasma and receptors of tissue fluids. The molecular weight ranging from 27 to 30 KD (Siham *et al*, 2016). Interleukins are

the most numerous cytokines, ranging from IL-1 to IL-35 and are divided into many smaller families (Baltimore *et al*, 2001). Interleukin-6, it is one of the most essential multifunctional cytokines with a molecular weight of 22-30 kilo Dalton. Many types of cells generate it, including active T and B lymphocytes, monocytes, macrophages, epithelial cells and meningeal cells in the brain (Stoll *et al*, 2002). Interleukin-6 (IL-6R) receptors are widespread in the body, as they are present on hematopoietic precursors, macrophages, myeloid cells, hepatocytes, and plasma cells (Brocklehurst *et al*, 2011). In sepsis, IL-6 is a key mediator during the acute phase of the inflammatory response several studies have looked at its therapeutic benefit in patients with different septic conditions (Paradkar *et al*, 2014 and Williams *et al*, 2012). Interleukin-11 is a protein that induces platelet synthesis (mega karyo cyto poiesis), as well as activating osteoclasts, inhibiting macrophage mediator production and epithelial cell apoptosis and proliferation. These roles may be especially significant in mediating interleukin 11's mucosal protective effects (Rajeswari *et al*, 2016 and Thandavan *et al*, 2015). Therefore, it is important to study the role of different types of interleukins in neonatal sepsis.

MATERIALS AND METHODS

Study design

This is case-control study was conducted convenience sampling was performed, all the information on patients and healthy infant were recorded through a personal interview with the mothers according to the questionnaire. IL-6 and IL-11 levels were determined using enzyme-linked immune sorbent assay in diagnosing NS, early onset sepsis (EOS) and late-onset sepsis (LOS). In the Department of Pediatric in AI-Batool Teaching Hospital, Diyala Governorate, Iraq for 6 month the period from 1 November, 2020 to 30th April, 2021.

Bacterial isolates

All the samples were entered into the Back Alert system to ensure that they were positive for bacterial growth and were incubated for various times. All isolates were diagnosed based on using conventional isolation and diagnosis methods and biochemical and bacteriological tests after cultured in the cultures media, and the isolates gave a positive results for these tests were confirmed using VITEK 2 compact system.

Immunological assays

The technique of Enzyme-linked immune sorbent assay (ELISA) was used to estimate the concentrations of cytokines in the serum of the studied samples as follows: Determination of interleukin-6 levels and determination of interleukin-11 levels.

Measurement of serum cytokine level

The level of cytokines was quantified using the adsorption test for immune antibodies binds to the enzyme (Sandwich ELISA test). For 196 samples, of which 100 were from patients and 96 samples from healthy ones, According to the instructions received examination kit in company (Demeditec) for IL-6 and a company (CUSABIO) for IL-11.

RESULTS

The bacterial isolated from neonates sepsis

From blood samples, the highest isolates was *Staphylococcus epidermidis* 26/60 (43.3%), followed by *Klebsiella pneumoniae* 13/60 (21.7%), *Staphylococcus aureus* 10/60(16.7%), *Pseudomonas aeruginosa* 8/60 (13.3%) and *Escherichia coli* 3/60 (5%) (Fig. 1). It was seems that neonates with EOS (0-7) days of age forming the highest rate (71.6%) of participants, while neonates with LOS (7-30) days of age forms (28.3%).

Concentration of Interleukin-6 in neonates with different causes of bacterial septicemia

The concentration of IL-6 in group of infected with septicemia showed differences significantly (P≤0.05)

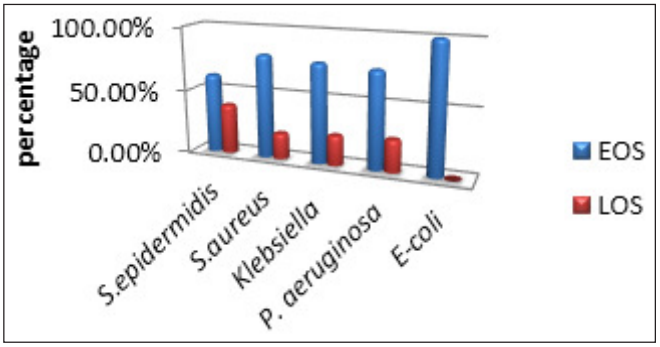

Fig. 1 : The bacterial isolated from neonates with different types of sepsis which include EOS: Early Onset Sepsis, and LOS: Late Onset Sepsis).

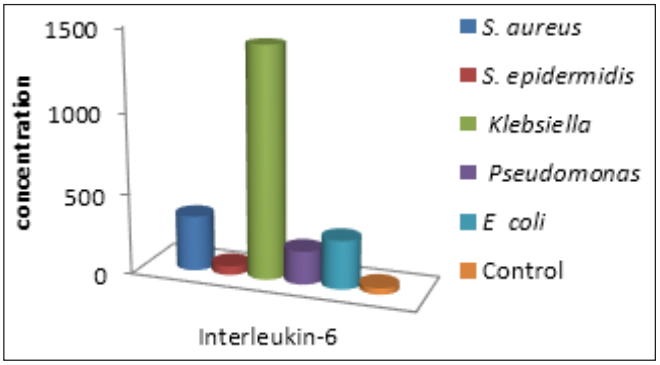

Fig. 2 : Interleukin-6 concentrations in children with different causes of septicemia.

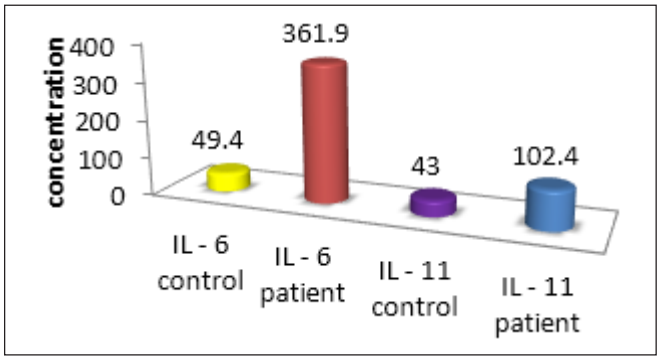

Fig. 3 : Represents the level of interleukin-6 and interleukin-11 in healthy and infected newborns with septicemia according to the types of sepsis.

according to different bacteria and compared with control group at (Mean±SE). The results revealed that the highest concentration of IL-6 in children infected with *Klebsiella pneumoniae* (1415.16 ± 513.81) then *Staphylococcus aureus* (343.25 ± 82.21) then *E coli and Pseudomonas aeruginosa* (298.66 ± 9.95 and 204.50 ± 0.500), respectively. While, there are non-significant differences (P≥0.05) in concentration of IL-6 in children infected with *Staph epidermidis* as compared with control group (54.88 ± 17.55 and 39.48 ± 2.97) respectively as shown in Fig. 2.

Estimating the concentration of interleukin-6 and interleukin-11

The results of interleukin-11 and interleukin-6 in serum showed a significant elevation at (P≤0.05) in levels of interleukin- 6 of infected with septicemia compared with levels of interleukin-11 at (mean ± SE) (Fig. 3). The concentration of IL-6 in groups of EOS and LOS showed significantly increasing (P≤0.05) compared with concentration of interleukin-11 at (Mean ± SE).

DISCUSSION

The results of our current study revealed that *S. epidermidis* was the most common Gram-positive bacteria isolate, accounting for 43.3 % of all isolates, and these findings are consistent with (Takahashi *et al*, 2016 and Leng *et al*, 1997) showed the *S. epidermidis* was major isolate, and disagree with Shrestha *et al* (2010) in India, which showed that the *Staphylococcus aureus* was the most prevalent, one explanation for the disparity may be the lack of compliance with infection prevention and control steps. The *Klebsiella pneumoniae* was the most common for Gram-negative bacteria isolate accounting for (21.7%) and this findings was similar with Sharma *et al* (2013) and Gyawali *et al* (2013), which showed the *Klebsiella pneumoniae* isolate accounts the highest, which causes infection in neonates. Geographical variations in the causative organism, as well as differences in the test climate, study population and hand hygiene habits, can explain the variation in the main isolate. The most common species linked to neonatal sepsis differ depending on when infections occur and where they occur according to Shrestha *et al* (2012) and Aftab *et al* (2007). In addition, the immune system of premature newborns is less able to prevent and destroy infection and as a result, they are more likely to develop early septicemia. The results of our study showed that the highest concentration of interleukin-6 was for *Klebsiella pneumoniae*, indicating that the concentration of interleukin-6 was higher for gram-negative bacteria compared to gram-positive bacteria, and these results are consistent with Shrestha *et al* (2007), which was found that the levels of interleukin-6 and CRP were higher in gram-negative bacteremia in the intensive care unit according to Abe *et al* (2010) and Kumar *et al* (2010), that showed the mean of IL-6 in infants with positive blood cultures was 117.49 pg/ml, and its level was substantially higher than two classes of infants with negative blood cultures having 2 to 3 signs of sepsis. The differences in IL-6 concentrations between neonates infected with different microorganisms could be due to differences in the host's inflammatory response during infection. These findings contradicted those of Webb *et al* (2008) and Lotze *et al* (2007), who observed that TNF levels were higher in newborns gram-negative bacteremia than in gram-positive bacteremia, but no difference in IL-6 and CRP levels in the study specimen's. The differences in interleukin-6 concentrations between bacterial isolates are due to differences in the bacteria's virulence mechanisms, which result in differences in the host's response, the degree of activation of various signaling cascades and the stimulation/inhibition of host cell apoptosis, all of which effect on the diagnosis linked to pathogens (Finlay *et al* (2006). The results of my current study showed a significant increase in the levels of interleukin-6 in the group of early onset sepsis patients (EOS) compared to the control group and this indicates the importance of the relationship between early onset sepsis and high levels of interleukin-6. IL-6 can be used as an independent predictor for predicting intrauterine chorionitis in pregnant mothers and cord blood, according to studies (Zhao *et al*, 2015 and Boskabadi *et al*, 2018). These results are similar to those of Benitz *et al* (2010) and Liu *et al* (2020), they found that interleukin-6 was significantly increased in the EOS group compared to the control group. The results of my current study showed that the levels of interleukin-11 was slight increase for this interleukin level in the group of sepsis patients compared to the control group and the levels of interleukin-

6. IL-11 stimulates the formation of primitive hematopoietic stem cells and lymphoid stem cells in bone marrow because it is an inhibitory factor (one of the inhibitory cytokines) and functions as an anti-inflammatory mediator inhibitory and multifunctional hematopoietic cytokine that originates from IL-1 stimulated primate stromal cell lines together with other cytokines (Chauhan *et al*, 2017 and Abdollahi *et al*, 2012). In addition IL-11 has been to suppress radiation-induced B-cell malignancies by increasing the radiation resistance of hematopoietic stem cells and restoring thrombocytopenia caused by bone marrow suppression, patients with sepsis also suffer from bone marrow suppression according to Wan *et al* (2014).

CONCLUSION

The findings revealed that neonatal EOS is more common than LOS in NICUs in Baquba city, Diyala Governorates. The results showed that IL-6 can be a reliable marker for predicting neonatal sepsis and can be used as a good guide for early detection of sepsis in neonatal care units, in comparison to blood culture whereas the blood culture technology (the gold standard) takes at least 24–48 hours and prenatal antibiotic use further reduces blood culture accuracy. IL-11 can help protect people with thrombocytopenia who are suffering from sepsis. The findings of this study suggested that IL-11 plays a protective role in sepsis patients with thrombocytopenia by accelerating platelet recovery and significantly reducing the extent of inflammatory responses, thus lowering mortality. The study found that the levels of the interleukins IL-6 and IL-11 levels increase in early time for inflammation, making them a good diagnosis marker for neonatal sepsis.

Ethical clearance

The project of this study was taken from the ethical committee of College of Medicine, University of Diyala.

Source of funding

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Conflict of interest

Nil

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