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Assessing the Role of Clinical Manifestations and Laboratory Findings in Neonatal Sepsis

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Abstract

Background: Neonatal sepsis is one of the major causes of morbidity and mortality in newborns. Since early diagnosis of neonatal septicemia is important for timely initiation of correct antimicrobial therapy and considering the existence of variability in non-specific clinical laboratories, we assessed the role of clinical manifestations and laboratory findings to find the right diagnosis.
Objectives: The aim of this study was to evaluate, record and rank the clinical manifestations and lab data of neonates with clinical sepsis.
Methods: In a cross sectional descriptive prospective study in 2013, a total of 110 consecutive infants with clinical manifestations of sepsis were studied in two groups including early onset sepsis (EOS) taking place at 72 hours of age or younger, and late onset sepsis (LOS) occurring after 72 hours. Check list of infant's data, presenting symptoms or signs and laboratory data in both groups were evaluated and recorded. Significant differences were set at as $P < 0.05$.
Results: Overall, 81.8% of infants had EOS while 18.2% of infants had LOS. The mean age at the time of EOS and LOS presentation was one to two days and four to twelve days, respectively. The most common clinical manifestations were respiratory distress in 49 (44.5%), jaundice in 28 (25.5%), vomiting in 26 (23.6%) and poor feeding in 23 (20.9%) of the infants. Other clinical manifestations were lethargy (weakness), decreased sucking reflex, fever, tremor, abdominal distention and seizure, found in 12 (10.9%), 10 (9.1%), 4 (3.6%), 4 (3.6%), 3 (2.7%) and 2 (1.8%) neonates, respectively. Early Onset Sepsis was considerably associated with respiratory distress ($P < 0.001$), while LOS in neonates was followed by jaundice ($P < 0.001$), seizure ($P = 0.02$) and fever ($P < 0.001$). Anemia, leukocytopenia, leukocytosis, thrombocytopenia and C-reactive protein (CRP) positive results and blood culture was detected in 36 (32.7%), 2 (1.8%), 0 (0%), 2 (1.8%), 19 (17.3%) and 110 (100 %) neonates, respectively. Cerebrospinal Fluid (CSF) cultures were negative in all infants. Positive urine culture was seen in 10 (9.1%) infants.
Conclusions: Respiratory distress is more common in EOS whereas jaundice, fever and seizure are more likely to be observed in LOS infants. Considering the results, clinical manifestations should be regarded as an important part of early diagnosis of sepsis.

Keywords: Infant, Leukocyte Count, Blood, Culture, Sepsis

1. Background

Neonatal sepsis causes high morbidity and mortality of newborns (1, 2). The world health organization (WHO) has estimated four million neonate deaths in the first four weeks of life, in which one million of them is allocated to neonatal sepsis with occurrence of 42% in the first week of life (3, 4). There are two classifications of sepsis including early onset sepsis (EOS), which presents within the first 72 hours of life, and late onset sepsis (LOS), which presents after 72 hours of life (5). Early onset sepsis is presumably due to parental risk factors due to bacteria acquired before and during delivery and overall maternal genital tract as the main source of infection (5, 6). Possible risk factors for EOS include low birth weight (LBW) (< 2500 grams) (7) or prematurity, maternal febrile due to bacterial infection during the two weeks before delivery, meconium stained liquor, prolonged rupture of membranes (PROM) for more than 18 hours and maternal chorioamnionitis or intraamniotic infection, which is defined as maternal leukocytosis (> 15000/mm), fever (> 38°C), uterine tenderness, tachycardia (> 100/min), fetal tachycardia (> 160/min) and purulent amniotic fluid (AF), prolonged labor, defined by more than 24 hours for each stage, and prenatal asphyxia (5, 6). Late onset sepsis is related to bacteria acquired after delivery from nosocomial or community sources (5). Very Low Birth Weight Infants (VLBW) have been admitted to neonatal intensive care unit (NICU) of hospitals for a long time; invasive procedures, non-hygienic behavior during and following the delivery are the main nosocomial infection risk factors (8). It has also been shown that within the first 72 hours of life, EOS is frequently associated with respiratory distress including difficulty in breathing and pneumonia, whereas LOS usually occurs with septicemia

and pneumonia, 72 hours after birth (6). Early Onset Sepsis is persistently associated with poor outcome, which is comparable with less frequent and severe outcome of LOS (9). Many studies were undertaken to introduce different hematological tests as well as simple tools for early diagnosis of neonatal sepsis. Early diagnosis and prompt treatment can improve our outcome in the management of newborns' sepsis. Blood culture as the gold standard for the definite diagnosis of sepsis is only obtainable after 48 to 72 hours (6), thus the other diagnostic methods such as C-reactive protein (CRP l) level and white blood cell (WBC) count, as laboratory tests, can assist in timely diagnosis of neonate sepsis (10). Symptoms of sepsis mainly include refusal for feed, lethargy and poor cry (6, 11). As the therapy should be started immediately in neonates suspected to have sepsis, only minimal and rapid investigations should be undertaken (6). However, there are some defects in laboratory tests such as low positive predictive value of CRP and CBC (12, 13).

2. Objectives

The aim of this study was to report our experience on clinical manifestations and laboratory data of 110 infants, who had EOS and LOS to assist in the early diagnosis of sepsis with the help of diagnostic value of clinical manifestations.

3. Methods

This cross-sectional descriptive prospective study was performed on 110 consecutive neonates (1800 to 5400 grams, mean = 3205 $\pm$ 650 grams, and 36 - 40 weeks) with clinical manifestations of sepsis, who were admitted to Javaheri hospital from January 2013 to October 2013. The study was approved by the ethical committee of Islamic Azad University research center and the protocol conformed with the ethical guidelines of the 1975 declaration of Helsinki. The study was initiated after written consent was obtained from parents or caretakers. Neonatal sepsis is a clinical syndrome, which is a general reaction to infection: Systemic Inflammation Response (SIR) and general damage of tissues. All patients must meet the following inclusion criteria for entry into the neonatal sepsis disease. Clinical signs including presence of respiratory distress, jaundice, vomiting, poor-feeding, lethargy (weakness), reduced sucking, fever, tremor, abdominal distention and seizure; laboratory findings including anemia, leukocytopenia, leukocytosis, thrombocytopenia, CRP, CSF culture, urine culture or two positive blood cultures within the 28 days of life, were the criteria for diagnosis of sepsis. Sepsis was diagnosed based on CRP, total leukocyte count (TLC), total neutrophil count (TNC), immature neutrophils to total neutrophil count ratio (I/T ratio), thrombocytopenia, two positive blood cultures within the 28 days of life in all neonates. Antibiotic therapy (ampicillin 50 mg/kg/dose q8 hr IV and cefotaxime 50 mg/kg/dose q12hr IV) was applied for all neonates. Neonates under antibiotic therapy, cases suspicious of sepsis with double-negative blood cultures prior to antibiotic therapy, and those with contaminated blood culture by commensal bacilli, were excluded from the study. Critically ill infants were followed up for clinical manifestations and complications and were treated based on the conventional approach. Chest X-ray (CXR) was done for all neonates for differential diagnosis, to rule out mimicked respiratory distress, such as transient tachypnea (TTN), Respiratory distress syndrome (RDS), meconium aspiration syndrome, congenital anomalies, pneumothorax, pneumomediastinum, and pleural effusion within the first few hours of life in neonates. Early onset sepsis and LOS were considered in neonates, who had clinical sepsis signs in the first 72 hours and after 72 hours of age, respectively. Data including birth weight, gestational age based on the first day of the mother's last menstrual period (LMP), sonographic information during pregnancy or Ballard's score for intrauterine age, gender of infant, mother's age, leukocytosis (WBC count > 35000), leukocytopenia (WBC count < 5000 mm^3), thrombocytopenia ($100 \times 10^3/\mu L$ or 100×10^9/L), anemia (venous Hemoglobin (Hb) concentration < 14.5 g/dL within 24 hours after birth) to exclude types of physiologic anemia, which varies from 14.6 to 22.5 g/dL at birth to a low of 10.0 to 12.0 g/dL from eight up to ten weeks, and positive CRP (> 5 mg/dL), were recorded.

3.1. Statistical Study

Data were analyzed by the Fisher's exact test, Chi-square and independent T-test by means of SPSS statistical software. Significant difference was set at $p<0.05$.

4. Results

Early Onset Sepsis in 90 neonates (81.8%) and LOS in 20 neonates (18.2%) were detected from a total of 110 neonates with confirmed sepsis diagnosis. The mean age at the time of EOS and LOS presentation was 1.02 $\pm$ 0.15 days (1 to 2 days) and 8.15 $\pm$ 4.12 days (4 to 12 days), respectively. One hundred and five newborn infants (95.5%) were full-term and the rest (4.5%) were preterm. The most frequent presentation was respiratory distress, which was observed in 49 cases (45.5%) (consisting of 44 full term neonates and 5 preterm neonates). Other main clinical manifestations

including jaundice, vomiting and poor-feeding, were observed in 28 (25.5%), 26 (23.6%) and 23 (20.9%) neonates, respectively. Lethargy was observed in 12 neonates (10.9%) and decreased suck reflex was detected in 10 neonates (9.1%). Four neonates (3.6%) had fever and four neonates (3.6%) had tremor. Abdominal distention and seizure were found in three (2.7%) and two neonates (1.8%), respectively. Anemia was detected in 36 (32.7%) and leukocytopenia in two neonates (1.8%). None of the neonates had leukocytosis while two neonates (1.8%) had thrombocytopenia. The I/T ratio, according to formula I: T ratio (immature forms) / (total neutrophils + immature forms), was measured to diagnose sepsis and the ratio was reported as < 0.02. Positive CRP result was reported in 19 neonates (17.3%) and both blood cultures were positive within 28 days of life in all neonates. Cerebrospinal fluid (CSF) cultures were negative in all infants. Positive urine culture was seen in 10 (9.1%) infants. Organisms isolated from blood cultures were *Escherichia coli* (*E. coli*) 48 (53.3%), *Klebsiella* 15 (16.6%), coagulase negative *Staphylococcus* 15 (16.6%) and Group B *Streptococcus* (GBS) 12 (13.3%) were the most common pathogens found in EOS whereas *E. coli*: 10 (50%), *Klebsiella* 7 (30%) and coagulase negative *Staphylococcus* 3 (15%) were common in LOS.

In this study, there was no meaningful statistical difference between EOS/ LOS and the infant's gender. All neonates with LOS were full-term, whereas all preterm neonates had EOS. In this study, EOS was considerably associated with respiratory distress ($P < 0.001$) while LOS in neonates was followed by jaundice ($P < 0.001$), seizure ($P = 0.02$) and fever ($P < 0.001$). The incidence of anemia in LOS and EOS was 60% and 27%, respectively. Although leukocyte and neutrophil count in EOS were higher than LOS yet a higher lymphocyte count was detected in LOS (Table 1). Positive CRP was more frequent among neonates with LOS compared with EOS (Table 1).

5. Discussion

The results of this study showed that the most common signs in neonates with sepsis were respiratory distress, jaundice, vomiting and poor feeding. In fact, respiratory distress was more common in EOS while jaundice, fever and seizure were associated with LOS. Respiratory distress and poor feeding were the most common signs reported in various studies (2, 14). It is presumed that there is an association between poor feeding and jaundice as common presentations of LOS. Following introduction of CRP and its role in duration of antibiotic therapy in neonatal sepsis (11), some studies were undertaken based on the relationship between CRP and septicemia. Berger et al. (15) compared the diagnostic value of CRP and WBC counts in EOS and LOS and introduced elevated CRP as the best particular test in early detection of both these complications. Furthermore, a number of studies showed the accordance of clinical manifestations and laboratory results in EOS and LOS (6, 9). Mannan et al. in 2010 (16), Chacha et al. in 2014 (17) and Hedegaard et al. in 2014 (18) showed elevated CRP level in neonates with sepsis. However, there were some disadvantages related to the use of CRP, such as lack of capacity in detection of a specific pathogen, positive predictive value (12) and inaccessibility in many developing countries (19). In this study, CRP positivity, which is most seen in LOS was 17.3% (19/110 neonates). These results are similar to that of Luck (20), who showed that the CRP concentration is low in the beginning of the infection. It was shown that most infants had clinical signs within the first 12 birth hours (21, 22) with a low positive prediction in CRP and CBC (12, 13, 23, 24). However, on the basis of our results, more accurate diagnosis of sepsis is attainable when considering clinical signs so that prompt antibiotic treatment is initiated. Selimovic et al. (25) emphasized that WBC > 26400 may predict EOS. Due to physiologic leukocytosis, which is usually observed in newborn infants related to stress of delivery and a low positive predictive value, we suggested that leukocytosis should not be considered as a specific test. Furthermore, Manucha et al. (10) introduced thrombocytopenia, band cell > 15% and the ratio of immature and mature neutrophil as indicators of sepsis. Although we did not find a noteworthy accordance between baby's gender, gestational age and two categories of sepsis, we proposed meaningful differences between LBW and EOS, despite the fact that Prasetsom et al. (26) reported that there was no agreement between EOS and LOS and birth weight. Jiang et al. (1) showed a relationship between LBW and LOS. Some authors believed that the incidence of LOS increased among LBWs (1, 27), however in this study LBW neonates were usually diagnosed as septicemia in the first 72 hours of life. This study indicates that common signs and laboratory data among neonatal EOS, are respiratory distress, leukocytosis and thrombocytopenia. On the other hand, through diagnosing neonatal LOS, patients are usually observed with jaundice, fever and seizure. Also anemia and positive urine culture are more associated with neonatal LOS (28). In conclusion, according to the difficulties in the diagnosis of neonatal sepsis and the importance of early diagnosis and timely initiation of treatment, clinical manifestations are an important part of early sepsis diagnosis. Additional studies with larger sample sizes are needed to further clarify clinical manifestations, which lead to early sepsis detection.

Table 1. Comparison of Frequency of Mean Birth Weight and Cell Count in Neonates With Early Onset Sepsis (EOS) and Late Onset Sepsis (LOS)

Cell Count	Type of Sepsis (Standard Deviation ± Mean)			
	Late Onset Sepsis	Early Onset Sepsis	P Value	Normal ranges
Birth weight, g	3490.5 ± 572	3141.9 ± 652	0.03	2500 - 4200
Leukocytes count, mm^3	8905.3 ± 3509	13852.8 ± 4543	> 0.0001	9 - 35,000
Polymorph nuclear count, mm^3	4185.3 ± 421	9419.4 ± 590	> 0.0001	
Lymphocyte count, mm^3	4452 ± 421	4017 ± 590	> 0.0001	2 - 11000
Band cell count, mm^3	89 ± 32	277 ± 41	0.33	< 15% of total leukocytes count
Amount of Hb, g/dL	13.5 ± 1.8	15 ± 2	0.002	14.6 to 22.5 g/dL at birth
				10.0 to 12.0 g/dL from 8 up to 10 weeks

Table 2. Comparison of Frequency of C-Reactive Protein Positivity in Neonates with Early Onset Sepsis (EOS) and Late Onset Sepsis (LOS)

CRP	Sepsis	
	Positive	Negative
Early onset sepsis	14.4%	85.6%
Late onset sepsis	30%	70%

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Footnotes

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Conflict of Interest: There was no conflict of interest in this study.

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