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Frequency of Coexisting Meningitis in Neonates Admitted with Late-Onset Sepsis in Nursery, MTI DHQ Hospital, Dera Ismail Khan

Ayesha Khan[1], Farmanullah Burki[1], Imran Khan[1*], Alina Yahya[1] and Oushna Khan[1]

[1]Department of Pediatrics, District Headquarters Hospital, Gomal Medical College, Dera Ismail Khan, Pakistan

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***Corresponding Author:**
Imran Khan
Department of Pediatrics, District Headquarters Hospital, Gomal Medical College, Dera Ismail Khan, Pakistan
drimranbettani2017@gmail.com

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ABSTRACT

Neonatal Late-Onset Sepsis (LOS) is a serious condition that can lead to co-existing meningitis, increasing the risk of long-term complications and mortality. Early diagnosis remains challenging due to non-specific clinical symptoms and limitations in performing Lumbar Punctures (LPs). **Objective:** To determine the frequency of co-existing meningitis in neonates with LOS and identify clinical and laboratory markers associated with it. **Methods:** Neonates aged ≥72 hours with signs of LOS were included. Demographic data, clinical symptoms, and laboratory parameters were recorded. A comparative cross-sectional study was conducted in the neonatal nursery of DHQ Hospital, MTI, Dera Ismail Khan. Blood samples were analyzed for C-Reactive Protein (CRP), White Blood Cell (WBC) count, and blood culture, while CSF analysis included WBC count, protein, glucose, and culture. Data were analyzed using SPSS version 25.0, with the Chi-square test used for categorical variables and independent t-tests for continuous variables. A p-value of <0.05 was considered statistically significant.**Results:** Among 95 neonates with LOS, 53.7% had meningitis. Lethargy (p = 0.024) and previous antibiotic use (p = 0.034) were significantly associated with meningitis, while other clinical signs showed no significant difference. CSF analysis revealed elevated WBC counts in meningitis cases, but CRP and blood WBC were not significantly different. **Conclusions:** Meningitis was frequent among neonates with LOS, with lethargy and prior antibiotic use as key risk factors. Early identification of these factors may aid in timely diagnosis and intervention. Further multi-center studies are recommended to validate these findings.

INTRODUCTION

Neonatal infections are a significant cause of morbidity and mortality worldwide, particularly in developing countries where healthcare resources and early diagnostic tools are often limited [1]. Out of these infections, Late-Onset Sepsis (LOS) is one of the concerning complications as it often leads to severe issues like meningitis [2]. Failure to diagnose or treat the disease on time can lead to the condition resulting in life-threatening issues such as severe health complications like death, neurological injury, developmental impairment, and more extremity [3]. Despite the advancements in nursing care for neonates, detection of meningitis in a septic neonate during the initial period remains a challenge. This is because clinical manifestations tend to be faint and are common with many other newborn pathologies. The clinical manifestations of LOS may vary across geographic regions, particularly in areas with limited healthcare resources where early signs of sepsis can be missed or attributed to other neonatal conditions. In low-resource settings, the absence of advanced diagnostics and delayed presentation often lead to underrecognition of subtle symptoms such as poor feeding and lethargy. The diagnostic criteria for neonatal meningitis depend on the evaluation of Cerebrospinal Fluid (CSF) obtained through Lumbar Puncture (LP) [4]. However, LP is frequently deferred or omitted, particularly in neonates with severe clinical conditions due to its

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invasive nature. This relies more on clinical and laboratory parameters which are not always specific to meningitis [5]. Diagnosing meningitis in neonates with LOS is particularly difficult due to overlapping symptoms with sepsis, such as irritability, poor feeding, and apnea. Invasive procedures like lumbar puncture are often delayed or avoided in critically ill neonates, leading to missed or late diagnoses. Moreover, limited access to laboratory testing in low-resource hospitals further complicates timely identification. These challenges underscore the need for standardized clinical criteria, prompt LP when feasible, and improved training for frontline healthcare staff in neonatal assessment. Numerous studies have analysed the association of neonatal sepsis and meningitis, paying attention to factors such as prematurity, low birth weight, prolonged hospitalisation, mechanical ventilation, and previous antibiotic therapy as probable risk factors [6, 7]. The reported incidence and risk factors differ tremendously from one geographic area to another, and also from one healthcare facility to another. This study attempts to bridge these gaps by determining the frequency of associated meningitis in infants diagnosed with LOS at a tertiary care hospital in Pakistan. The prevalence of meningitis in neonates with LOS can differ considerably between regions due to variations in diagnostic capabilities, antibiotic stewardship practices, and access to specialized neonatal care. These contextual differences must be considered when interpreting findings across different healthcare settings. This study enhances early risk assessment through timely diagnosis, intervention, and more neonatal care protocols by identifying the clinical and laboratory parameters associated with neonatal meningitis.

These results will also be useful in improving strategies in the stewardship of antibiotics to minimise their indiscriminate use, which worsens neonatal infections and antibiotic resistance.

METHODS

This comparative cross-sectional study was conducted at the Neonatal Nursery of DHQ Hospital, Medical Teaching Institution (MTI) Dera Ismail Khan, from June 1, 2024, to November 31, 2024, to determine the frequency of coexisting meningitis in neonates admitted with Late-Onset Sepsis (LOS) and assess associated clinical and laboratory parameters. The Ethical Review Committee of Gomal Medical College, D.I. Khan, granted ethical approval with reference: 33/GJMS, dated 24th March 2023. The synopsis was also approved by the Research Evaluation Unit of the College of Physicians and Surgeons Pakistan with reference: CPSP/REU/PED-2022-029-6854, dated 1st June 2024. The ssample size of 95 neonates was calculated using Open Epi software, considering a 95% confidence level, 80% power, and an expected prevalence of 50% for meningitis among neonates with LOS, based on the findings of Nafis *et al.*, who reported a similar frequency in a comparable study setting [8].Inclusion criteria involved neonates aged ≥72 hours admitted with clinical signs of LOS, including fever, lethargy, poor feeding, respiratory distress, and seizures.Neonates with congenital anomalies or pre-existing neurological conditions were excluded. Clinical signs were documented using a structured assessment form.Lethargy was defined as reduced spontaneous movement and diminished response to handling or external stimuli, while poor feeding was defined as refusal of at least two consecutive feeds within a 12-hour period, as reported by nursing staff and confirmed by the attending pediatrician.All data were recorded by trained personnel using predefined operational definitions to minimize observer bias and ensure consistency across cases.After obtaining informed consent, the following investigations were performed: Blood culture using the BacT/ALERT system, processed under aseptic conditions. Blood samples were drawn using sterile gloves, alcohol swabs, and closed system vacutainers to avoid contamination. Gram staining and biochemical tests were used for organism identification.CRP and WBC counts were measured using standardized automated analyzers. Lumbar Puncture (LP) was performed under sterile conditions by a trained pediatrician. Sterile drapes, gloves, and single-use spinal needles were used during the LP procedure. CSF samples were immediately transferred into sterile containers and sent to the lab without delay to minimize contamination risk. CSF analysis included: Total leukocyte count (manual Neubauer chamber). Protein and glucose (biochemical autoanalyzer).CSF culture (chocolate and MacConkey agar).The microbiology lab followed established infection control protocols for sample handling and culture processing. To ensure reliability, all laboratory procedures were conducted using standardized techniques, and equipment calibration was regularly performed. Quality control protocols were followed rigorously in the microbiology lab to avoid contamination during blood and CSF culture processing. Blood samples were collected under aseptic conditions, and lumbar punctures were performed by trained pediatricians using sterile technique to minimize contamination risk. All laboratory analyses were performed in a controlled environment using calibrated and quality-checked equipment. Validity was enhanced by using established clinical and laboratory criteria for diagnosing LOS and meningitis. Late-Onset Sepsis (LOS) was defined as sepsis occurring after 72 hours of life, with signs including fever, lethargy, poor feeding, respiratory distress, and seizures. Meningitis was diagnosed based on CSF findings, including elevated WBC count (>30 cells/mm^3), elevated protein, decreased glucose, or positive CSF culture, as per standard neonatal infection guidelines. Standard definitions and protocols were followed during patient assessment and

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sample collection to maintain consistency in data collection.Selection bias was minimized by applying clear inclusion and exclusion criteria, ensuring that only neonates meeting the defined eligibility were enrolled. Data were analysed using SPSS version 25.0.The Chi-square test was applied to compare categorical variables such as gestational age, birth weight, gender, prolonged hospital stay, mechanical ventilation, and prior antibiotic use between neonates with and without meningitis. For continuous variables such as CRP, WBC count, CSF WBC, CSF protein, and CSF glucose, an independent t-test was used to determine statistical significance. A p-value of <0.05 was considered statistically significant.The frequency of meningitis among neonates with LOS was recorded. Secondary outcomes included NICU admission rates and mortality among affected neonates. The results were presented in the form of tables and graphs to illustrate key findings.

RESULTS

The analysis of demographic and clinical characteristics of neonates with LOS showed no significant associations with meningitis. Preterm neonates had a slightly higher occurrence of meningitis compared to term neonates, but the difference was not statistically significant. Similarly, low birth weight infants (<2.5 kg) and those with a birth weight of ≥2.5 kg showed nearly equal distribution between meningitis-positive and meningitis-negative groups. Gender also did not play a significant role in meningitis occurrence, with both males and females showing similar proportions. These findings suggest that general demographic factors alone may not strongly predict meningitis risk in neonates with LOS.

Table 1: Demographic and Clinical Characteristics of Neonates with LOS

Variables	Meningitis		p-Value
	Present Frequency (%)	Absent Frequency (%)	
Gestational Age			
Preterm	33 (56.9%)	25 (43.1%)	0.432
Term	18 (48.6%)	19 (51.4%)	
Birth Weight			
<2.5 kg (LBW)	32 (52.5%)	29 (47.5%)	0.748
≥2.5 kg	19 (55.9%)	15 (44.1%)	
Gender			
Male	20 (55.6%)	16 (44.4%)	0.775
Female	31 (52.5%)	28 (47.5%)	

Among the clinical variables assessed, lethargy and previous antibiotic use were found to have a statistically significant association with meningitis. Neonates with meningitis had a higher prevalence of lethargy, indicating that this symptom might be an important early indicator of infection. Previous antibiotic use was also more frequent in neonates diagnosed with meningitis, suggesting a possible link between prior antibiotic exposure and increased susceptibility to meningitis. Other clinical features, including fever, poor feeding, respiratory distress, seizures, prolonged hospital stay, and mechanical ventilation, were not significantly associated with meningitis. Although these symptoms were common in neonates with meningitis, they were also observed in those without the condition, making them less specific for meningitis diagnosis.

Table 2: Clinical Presentation and Outcomes of Neonates with Meningitis

Clinical/Outcome Variables	Meningitis		p-Value
	Present Frequency (%)	Absent Frequency (%)	
Fever	32 (55.2%)	26 (44.8%)	0.716
Lethargy	40 (61.5%)	25 (38.5%)	0.024 (Significant)
Poor Feeding	32 (55.2%)	26 (44.8%)	0.716
Respiratory Distress	28 (54.9%)	23 (45.1%)	0.798
Seizures	31 (54.4%)	26 (45.6%)	0.867
Prolonged Hospital Stay (≥7 Days)	34 (55.7%)	27 (44.3%)	0.591
Mechanical Ventilation	37 (53.6%)	32 (46.4%)	0.984
Previous Antibiotic Use	44 (59.5%)	30 (40.5%)	0.034 (Significant)

The laboratory findings did not reveal any significant associations between meningitis and most biochemical parameters. The mean CRP levels and WBC counts were slightly elevated in neonates with meningitis compared to those without, but the difference was not statistically significant. The CSF WBC count, an important indicator of infection, was higher in the meningitis group, though it did not reach statistical significance. CSF protein and glucose levels showed no meaningful differences between the two groups. Similarly, blood and CSF culture positivity did not differ significantly, suggesting that these tests alone may not be reliable predictors of meningitis in neonates with LOS.

Table 3: Laboratory Findings in Neonates with and without Meningitis

Laboratory Test	Meningitis		p-Value
	Present Mean ± SD/ Frequency (%)	Absent Mean ± SD/ Frequency (%)	
CRP (mg/L)	17.53 ± 5.91	16.84 ± 7.09	0.604
WBC Count (/mm^3)	18,061.53 ± 4,981.47	18,561.35 ± 5,942.80	0.657
CSF WBC Count (/mm^3)	159.24 ± 66.44	136.80 ± 62.76	0.096
CSF Protein (mg/dL)	207.39 ± 79.41	198.25 ± 62.03	0.538
CSF Glucose (mg/dL)	36.91 ± 13.50	37.26 ± 12.44	0.897
Blood Culture Positive	32 (58.2%)	23 (41.8%)	0.303
Blood Culture Negative	19 (47.5%)	21 (52.5%)	
CSF Culture Positive	33 (53.2%)	29 (46.8%)	0.902
CSF Culture Negative	18 (54.5%)	15 (45.5%)	

The final table examined neonatal outcomes, including NICU admission and mortality, in relation to meningitis. Although a higher percentage of neonates with meningitis required NICU admission compared to those without, the

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association was not statistically significant.Similarly, mortality was observed more frequently in the meningitis group, but the difference did not reach significance. These findings suggest that while meningitis can contribute to more severe illness and the need for intensive care, other underlying factors may also influence neonatal outcomes.

Table 4: Outcomes of the Characteristics

Outcome Variables	Meningitis		p-Value
	Present Frequency (%)	Absent Frequency (%)	
NICU Admission	40 (55.6%)	32 (44.4%)	0.518
No NICU Admission	11 (47.8%)	12 (52.2%)	
Mortality	42 (56.8%)	32 (43.2%)	0.260
Survival	9 (42.9%)	12 (57.1%)	

Overall, this analysis highlights that while some clinical indicators, such as lethargy and previous antibiotic use, showed significant associations with meningitis, most demographic, laboratory, and outcome variables did not. These results emphasize the complexity of diagnosing and managing meningitis in neonates with LOS and suggest the need for a combination of clinical, laboratory, and microbiological markers to improve early identification and treatment strategies. Figure 1 illustrates a clustered bar chart that highlights lethargy and prior antibiotic use in the neonates with and without meningitis. It shows that 40 lethargic neonates had meningitis, while 25 had non-meningitis. The data also indicate that, similarly, 44 neonates with meningitis had previous antibiotic use and 30 without. These findings implicate the importance of careful surveillance of the neonates exhibiting these risk factors to enhance the early diagnosis of meningitis and its management.

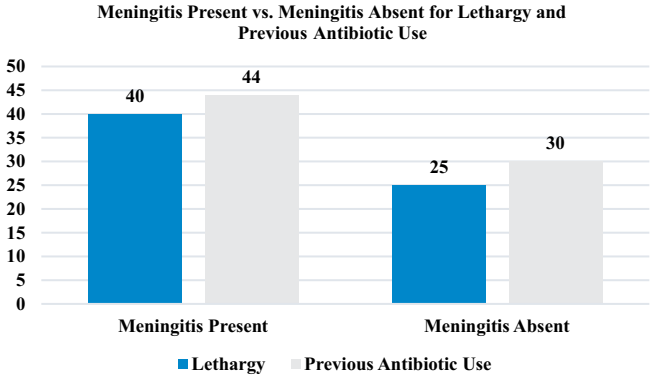

Figure 1: The clustered bar chart illustrates the comparison of lethargy and previous antibiotic use among neonates diagnosed with meningitis and those without the condition.

DISCUSSION

The results of this research shed light on the dual presence of meningitis in neonates with LOS. Infections during the neonatal stage continue to be one of the major causes of morbidity and mortality, most notably among developing nations with inadequate health care facilities. The recognition of clinical and laboratory indicators linked with neonatal meningitis was important in enhancing early diagnosis and improving outcomes. The analysis found a notable relationship between lethargy, previous antibiotic treatment, and the occurrence of meningitis in neonates with LOS. These findings were in line with earlier studies which emphasised that patients suffering from infection of the central nervous system often show signs of altered mental status and poor activity levels [8-10]. The study showed that strong early signs of neonatal meningitis included irritability and reduced responsiveness [11-13]. Other studies have also shown that neonates with poor feeding coupled with lethargy are likely to have underlying central nervous system infections [13-15]. A notable association was found concerning the use of antibiotics and the occurrence of meningitis. This was in accordance with reports by other authors who stated that prior antibiotic therapy might modify microbial flora and could be responsible along with other factors for the development of resistant organisms which increases the probability of invasive infections [16-18]. The empirical use of antibiotics in neonates may be capable of masking early signs of meningitis by partially treating bloodstream infections and, thus, delaying a definitive diagnosis. This highlights the importance of judicious antibiotic use in neonatal sepsis management. Moreover, early antibiotic exposure may partially treat systemic infections, thereby reducing the clinical visibility of hallmark signs like lethargy or irritability. This can lower the sensitivity of these signs for diagnosing meningitis, potentially delaying lumbar puncture or leading to under diagnosis. Therefore, early consideration of LP before antibiotic administration is crucial, especially in neonates showing subtle signs suggestive of central nervous system involvement. Although other clinical factors such as prolonged hospital stay, mechanical ventilation, fever, and respiratory distress were not significantly associated with meningitis in this study, they have been widely reported as risk factors in previous research. Studies found that neonates requiring mechanical ventilation or prolonged hospitalization had a higher risk of meningitis, often due to increased exposure to hospital-acquired infections [14, 19]. The lack of significant association in our findings may be due to the relatively small sample size, which limited statistical power, and the presence of confounding variables that were not controlled for, such as comorbidities and severity of illness. Hence, these findings should be interpreted cautiously, and larger multi-centre studies are warranted to validate these associations. Laboratory findings in this study also showed higher CSF WBC counts in neonates with meningitis, which aligns with the established diagnostic criteria for bacterial meningitis. While CRP and WBC counts were not significantly different, CSF protein levels were slightly elevated in the meningitis group, supporting studies reported that CSF protein elevation is a common marker in neonatal meningitis [20, 21]. CSF WBC count, in

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particular, may serve as an important early screening tool in neonates suspected of meningitis, especially when clinical symptoms are masked or unclear. A significantly elevated CSF WBC, even in the absence of culture positivity, should prompt early therapeutic intervention. This parameter can be crucial for timely decision-making in resource-limited settings where advanced diagnostics may not be readily available. The strengths of this research include targeting a high-risk population, applying standard diagnostic techniques, and integrating clinical with laboratory parameters. Nevertheless, some limitations need to be addressed. The sample was small and could have weakened the statistical power of several associations. Furthermore, the investigation was single centre, which limits extrapolation to other neonatal units that have differing patient populations and antibiotic control practices.

CONCLUSIONS

Meningitis was found to be a frequent coexisting condition in neonates with late-onset sepsis. Among various clinical and laboratory variables, lethargy and prior antibiotic use were significantly associated with the presence of meningitis. These findings highlight the importance of early recognition of subtle clinical signs and the judicious use of antibiotics in neonatal care. Routine consideration of lumbar puncture in neonates with LOS, particularly those presenting with lethargy or previous antibiotic exposure, may improve early detection and treatment outcomes. Further multi-centre studies with larger sample sizes are recommended to validate these associations and inform clinical guidelines.

Authors Contribution

Conceptualization: IK

Methodology: AK, FB, AJ, OK

Formal analysis: IK

Writing, review and editing: AK, FB, IK, AJ, OK

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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