ABSTRACT

Objectives: The objective of this study was to estimate the prevalence of meningitis in cases with late onset septicemia (LOS).

Materials and Methods: A prospective study was carried out for a period of 1 year in a tertiary care hospital in North West India to estimate the prevalence of meningitis in cases of LOS. In all the admitted neonates with features of sepsis with a positive C-reactive protein, a lumbar puncture (LP) was carried out and results interpreted on the basis of cerebrospinal fluid (CSF) cytology and biochemistry. Simultaneous blood and CSF cultures were also taken. All other baseline investigations were performed and in those diagnosed as meningitis an ultrasound head was carried out prior to discharge. No urine cultures were obtained.

Results: The study showed the prevalence of meningitis as 22.5% in neonates with LOS with statistically significant implications of meningitis versus gestation, sex, acquired the place of infection, and outcome in terms of sequelae/mortality.

Conclusions: Meningitis is commonly associated with late onset sepsis hence LP should be the standard of care in such neonates as the treatment protocol and the outcome is directly proportional to the diagnosis at initial presentation.

Key words: Late onset sepsicaemia, meningitis, neonates

INTRODUCTION

Invasive neonatal infections are important causes of mortality and morbidity in newborn infants all over the world including the industrialized countries with high hygienic standards, deliveries at hospitals, access to antimicrobial agents for prophylaxis, treatment, and facilities for advanced intensive care. Most studies of incidence and etiology of neonatal sepsis and meningitis come from these countries although there is a lack of data from the developing countries where the mortality and morbidity are probably immense.

Sepsis is responsible for about 30-50% of the total neonatal deaths in developing countries. The incidence of neonatal sepsis according to the data from National neonatal perinatal database is 30/1000 live births. The database comprising 18 tertiary care neonatal units across India found sepsis to be one of the most common causes of neonatal mortality contributing to 19% of all neonatal deaths. Septicemia was the most common clinical category with incidence of 23/1000 live births while the incidence of meningitis was reported to be 3/1000 live births. Late onset septicemia (LOS) usually presents after 72 h of age. Any newborn with bacterial sepsis is also at risk of meningitis. As such the incidence of meningitis in neonatal sepsis has varied from 0.3% to 3% in various studies, but LOS has been reported to be fairly associated with meningitis; with percentage ranging from 3% to 30%. Hence, the work-up for any newborn with signs of infection should include a spinal tap.

Keeping this in view a study to evaluate the Importance of obtaining lumbar puncture (LP) in neonates with LOS was planned.

MATERIALS AND METHODS

The study, observational in nature, was conducted on neonates admitted in the division of neonatology, department of pediatrics, of a tertiary care hospital in North-West India. All neonates with features of sepsis with a positive C-reactive protein were included in the study. A lumbar puncture was carried out and results interpreted on the basis of cerebrospinal fluid (CSF) cytology and biochemistry. Simultaneous blood and CSF cultures were also taken. All other baseline investigations were performed and in those diagnosed as meningitis an ultrasound head was carried out prior to discharge. No urine cultures were obtained.

Conclusions: Meningitis is commonly associated with late onset sepsis hence LP should be the standard of care in such neonates as the treatment protocol and the outcome is directly proportional to the diagnosis at initial presentation.

Key words: Late onset sepsicaemia, meningitis, neonates
northwest India over a period of 1 year from November 2008 to October 2009.

**Inclusion criteria**
- Neonates older than 72 h with signs and symptoms suggestive of sepsis viz:
  - Clinical features of sepsis, i.e., physical examination demonstrating either circulatory, respiratory, Central Nervous System (CNS) dysfunction or other features of sepsis
  - Circulatory dysfunction was evident by the presence of tachycardia (heart rate more than 160/min) or bradycardia (heart rate less than 100/min) or capillary refill time more than 3 s
  - Respiratory dysfunction was evidenced by the presence of grunting, flaring, retractions, tachypnea (respiratory rate more than 60/min) or apnea lasting more than 20 s
  - CNS dysfunction was evidenced by the presence of excessive crying, high pitched cry, bulging fontanels and/or occurrence of/or history of convulsions
  - Other symptoms/signs of sepsis included were; Lethargy, reduced feeding ability, no spontaneous movement, temperature more than 38°C, hypothermia, cyanosis, abdominal distension, increased pre-feed aspirates in pre-terms/Low Birth Weight, pustular lesions, umbilical sepsis.
  - Positive C-reactive protein (CRP).

**Exclusion criteria**
- Patients with spina bifida
- Anencephaly, other neural tube defects
- In very sick neonates, after initial stabilisation.

**Definitions used**
- Hospital acquired infection: Those neonates who were aseptic (CRP negative) at admission to the hospital.
- Those who developed sepsis during hospital stay/or presented within 1 week of discharge from the hospital (CRP positive).

- Community acquired infection: Those neonates who reported from the community at the first visit and were having features of sepsis at presentation (CRP positive).

In each neonate with clinical features of sepsis, a detailed history and examination was carried out as per a structured performa.

Neonates with features of sepsis and positive CRP (done as a qualitative estimation as positive/negative with the help of latex slide agglutination test) were subjected to the following investigations:
- LP (included cerebrospinal fluid (CSF) cytology, biochemistry and culture)
- Blood culture (1 ml sample of blood was collected under all aseptic precautions by veni-puncture and placed in a pediatric blood culture bottle containing tryptic soya broth)
- Complete blood count (including band cell count)
- Blood sugar, serum bilirubin (when required on clinical suspicion), and Renal function tests
- Chest X-ray.

Meningitis was labelled in a neonate whose CSF findings satisfied all the following criteria:
- CSF glucose less than the plasma glucose (sample was taken 30 min prior to LP) by ≥50%
- CSF white cell count >10/cumm
- CSF protein >80 mg/dl.
- With/without CSF culture positive.

Other investigations such as liver function tests, Prothrombin Time Index (PTI), arterial blood gas analysis, computed tomography/magnetic resonance imaging brain were carried out as and when required.

Ultrasonography of head was carried out in all patients with meningitis, at the time of discharge.

The neonates were followed-up, to determine their final outcome.

**Statistical analysis**
The data were analyzed with the help of computer software Epi-Info version 6.0.1 and SPSS 10.0 for Windows. Chi-square test was used to ascertain statistical significance among the proportions. Prevalence along with 95% confidence limits was calculated to express the magnitude. Odd’s ratio with 95% confidence limits was estimated vis a vis the presence or absence of meningitis in late onset neonatal sepsis. A $P<0.05$ was considered as statistically significant unless proved otherwise.

**RESULTS**
Mean weight was 2.515 kg with a standard deviation of 0.606 kg. Majority (51.8%) of the neonates came under the normal weight group while 41.8% constituted the low birth weight group and only 6.4% were in the Very Low Birth Weight group. The sex distribution in the study group was equal with males and females being 51 each with a sex ratio of 1. Demographic profile of cases is depicted in Table 1. The mean age of presentation of LOS in the hospital acquired group was 5.73 days with a standard deviation of 2.85 days.
vis $5.73\pm2.85$ and that in the community acquired group was $15.93\pm6.27$ days respectively.

Out of 102, 23 were having meningitis, which corresponded to 22.5% prevalence in this study with a 95% confidence interval of 14.4-30.6. Hospital acquired versus community acquired meningitis vis a vis the age at presentation is depicted in Table 2.

Clinical presentation of neonates with meningitis is depicted in Table 3. The statistical correlation with respect to the various factors in the meningitis versus no meningitis group is depicted in Table 4. The blood culture isolates in the septic neonates is depicted in Table 5 with CSF culture being sterile in all cases with meningitis diagnosed as per the criteria mentioned above.

**DISCUSSION**

In the present study, 22.5% (23/102) of neonates with LOS had meningitis. Almost comparative observation was reported by Visser and Hall where in the prevalence of meningitis in septic neonates with LOS was 24%.\[^{[15]}\] Schwersenski et al. and Hristeva et al. reported the prevalence of meningitis in LOS as 3.5% and 6.8% respectively, but the former excluded neonates more than 72 h and less than 7 days from their study and the latter delayed the LP procedure in all the babies who had respiratory distress.\[^{[11,16]}\] Kenyan study, Brazilian study and Asian study conducted by various authors reported prevalence of meningitis in neonates as 17.9%, 17% and 17.2% respectively.\[^{[17-19]}\] However, Brazilian study included both early and late onset cases of septicemia.\[^{[18]}\] These variations in the prevalence could be explained on the basis of the fact that meningitis was diagnosed in all these studies on the basis of CSF culture positivity alone.

In the present study, the LBW neonates with sepsis were 45.1% and pre-terms with sepsis were 21.6%. Out of neonates having meningitis 52.2% were pre-term and 47.8% were term. This high prevalence of meningitis in LBW and especially pre-term has also been reported by various studies.\[^{[17,20,21]}\] In the Brazilian study, it was observed that 81% of neonates with meningitis were pre-term, which appears to be due to the fact that he involved both Early Onset Septicemia (EOS) and LOS cases in his study.\[^{[18]}\] In a study performed at Taiwan, it was observed that LOS was significantly more common in VLBW and pre-term neonates.\[^{[13]}\]

Out of all the neonates having meningitis in the present study, 73.9% and 26.1% were males and females respectively and this difference was statistically significant. For pre-terms, the same data extrapolated wasn’t statistically significant. This difference in the pattern of observance can be explained on the basis of better available neonatal intensive care set up and early initiation of the drug therapy based on the available sensitivity reports. In the present study, meningitis was more frequently observed in the hospital acquired group as compared to the community acquired group (33.9% and 10.2% respectively), the difference being statistically significant. The mean age of presentation in hospital acquired LOS was $5.73 \pm 2.85$ days.

### Table 1: Profile of patients presenting with late onset septicemia

| Parameter  | Number (n = 102) (%) |
|------------|----------------------|
| Weight (kg) |                      |
| <1.5       | 7 (6.9)              |
| 1.5-2.5    | 46 (45.1)            |
| >2.5       | 49 (48)              |
| Sex        |                      |
| Male       |                      |
| Term       | 41 (40.2)            |
| Pre-term   | 10 (9.8)             |
| Female     |                      |
| Term       | 39 (38.2)            |
| Pre-term   | 12 (11.8)            |
| Age of presentation (days) |          |
| 3-7        | 46 (45.1)            |
| 8-12       | 18 (17.6)            |
| 13-17      | 14 (13.7)            |
| 18-22      | 17 (16.7)            |
| 23-27      | 7 (6.9)              |

### Table 2: Age of presentation vis a vis the hospital acquired versus community acquired group and meningitis and no meningitis group

| Age of presentation (days) | Hospital acquired | Community acquired |
|---------------------------|------------------|--------------------|
|                           | Meningitis n (%) | No meningitis n (%) |
|                           | Meningitis n (%) | No meningitis n (%) |
| 3-7                       | 15 (14.8)        | 31 (30.4)          |
|                           | Nil              | Nil                |
| 8-12                      | 2 (1.9)          | 4 (3.9)            |
|                           | 2 (1.9)          | 10 (9.8)           |
| 13-17                     | 1 (1)            | 0                  |
|                           | 1 (1)            | 12 (11.8)          |
| 18-22                     | 0                | 0                  |
|                           | 2 (1.9)          | 15 (14.8)          |
| 23-27                     | 0                | 0                  |
|                           | 7 (6.9)          |                    |

### Table 3: The signs/symptoms in cases with meningitis

| Symptom/sign               | Percentage |
|----------------------------|------------|
| Lethargy                   | 100        |
| Seizures                   | 92         |
| Fever                      | 49         |
| Refusal/decreased feeding  | 46.2       |
| Respiratory signs          | 25         |
| Abdominal distention       | 21         |
| Shock/sclerema             | 11         |
and that in community acquired group was 17.93 (±7.34) days. Similar observations were observed in a Chinese study for community acquired LOS (16±7 days). The mean age of presentation of cases of meningitis was 5.64 (±3.47) days in the hospital acquired group and 11.55 (±7.2) days in community acquired group with a mean age of presentation of cases of meningitis as 8.6 (±5.33) days as a whole.[16] The delayed age of presentation of community acquired meningitis was possibly due to the poor health-care seeking behavior in the community. However, in a study performed at Kenya the mean age of the presentation was 4.1 days, but their study included both EOS and LOS cases.[17]

Out of the neonates having meningitis, 26.1% expired (6/23) in the present study which lies almost in the middle of the range as compared to the observations made by Tiskumara et al. who observed in their study that meningitis is associated with mortality of 20% viz a viz a much higher mortality rate in the meningitis group, i.e., 37.7% and 37.5% as reported by Longe et al. and Hoque et al. respectively. However, in both these studies EOS group was also included along with LOS group.[19,20,23]

Sequela in the form of hydrocephalus was observed in 13% (3/23) cases of meningitis cases. The combined recovery versus sequelae/death risk in cases of meningitis was 60.9% and 39.1% versus 86.1% and 13.9% in those without meningitis respectively, the comparisons being statistically significant. In the present study, the combined risk of mortality/sequela is still high about 39.1%, whereas Bennhagen et al. in their study conducted in Sweden had observed that the combined mortality and handicap rates had decreased from 34% in 1976 to 15% in 1983.[24] This is probably because of their fast improving intensive care facilities. Al-Harthi et al. had observed mortality of 48% in neonatal meningitis, but they included EOS cases also and meningitis was documented only on CSF culture positivity.[25]

CONCLUSIONS

Meningitis is a major association with LOS cases. It is associated with significant morbidity and mortality and entails a prolonged antibiotic course. Thus, it is concluded that a LP is important in the evaluation of LOS cases and should be the standard of care in its management.

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