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Incidence, Clinical Profile and Etiology of Meningitis in Term Neonates with Clinical Sepsis

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ABSTRACT

Background: Sepsis is the commonest cause of neonatal mortality globally and is responsible for about 3–50% of the total neonatal deaths in the developing countries. Meningitis complicates 20% cases of early-onset and 10% cases of late onset sepsis. Although the mortality of neonatal bacterial meningitis has declined from 60% in early 1950-60s to around 10%, the morbidity is still as high as 50% in the survivors. So, it is important that neonatal meningitis must be diagnosed as early as possible.
Objective: To determine the incidence of meningitis in term neonates with clinical sepsis.
Materials and methods: Prospective hospital based time bound study conducted at Paediatric Department, limerick regional Hospital from 01-01-2013 to 31-12-2013.Term neonates admitted to NICU, limerick regional Hospital with "clinical sepsis" were evaluated and a set of investigations in relation to sepsis were done.
Lumbar puncture was performed and CSF was subjected for cytological and biochemical analysis for diagnosis of meningitis.
Statistical analysis: Data was entered in Microsoft Excel 2013analysed using SPSS software for Windows, version 22.0 and categorical tables, mean, median, Chi-square values, p value and the results correlated.
Results: In newborns with clinical sepsis (100 cases), meningitis was diagnosed in 9 (9%) cases, who met CSF cytological and biochemical criteria. CSF culture was positive in 6(33.33%) meningitis cases.
Conclusion: Meningitis was diagnosed in 9% clinical sepsis cases. There was a male preponderance. Meningitis was common in late onset sepsis cases. More multi-centric studies are required to revise the CSF cytological criteria for meningitis diagnosis.

Keywords: Neonatal Meningitis; Term neonates; Clinical sepsis; CSF analysis

INTRODUCTION

Sepsis is the commonest cause of neonatal mortality globally and is responsible for about 3-50% of the total neonatal deaths in the developing countries. In England and Wales, two population-based neonatal meningitis studies were conducted in the 1980s and 1990s and reported similar incidence rates of 0.22 and 0.21 per 1000 live births, respectively.[1,2] These rates are comparable to those of other European countries,[3] but lower than studies reported from Africa and Asia.[4] Although in the United Kingdom the case fatality associated with neonatal meningitis declined from 25% to 10% between the 1980s and 1990s,[1,2] long-term sequelae rates did not change, with up to 50% of survivors having long-term neurodevelopmental complica-tions. [5,6]

The subtle signs of septicaemia are common to various illnesses; therefore, clinical diagnosis of neonatal septicaemia is very difficult.[7] Meningitis complicates 20% cases of early-onset and 10% cases of late-onset sepsis.[8] The risk increases with decreasing gestational age and preterm infants carry two or three times the risk that term infants do and account for an even greater majority of the late-onset cases.[9]

Most cases of neonatal meningitis have associated arachnoiditis, vasculitis and

superficial thrombophlebitis. Ventriculitis occurs in 70-90% of the cases. Severe encephalopathic changes often occur, which may result in widespread cerebral atrophy. Hydrocephalus occurs in one third of cases, during second week of illness.

There can be associated suppurative ventriculitis which progresses to periventricular abscess formation. Bacterial meningitis is also the single most important cause of acquired sensorineural hearing loss.[10]

Although the mortality of neonatal bacterial meningitis has declined from 60% in early 1950-60s[11] to around 10%,[2] the morbidity is still as high as 50% in the survivors.[12] So, it is important that neonatal meningitis must be diagnosed as early as possible on the basis of the 'soft' signs of early neonatal infection such as temperature changes, jaundice, apnea, tachypnea and tachycardia. By the time bulging fontanel, high pitched cry, altered consciousness or seizures occur; the disease would have advanced to a stage where permanent neurological sequelae are more likely.[10]

In spite of the development of the rapid diagnosis of pathogens and new antibiotics, neonatal meningitis contributes to neonatal mortality and morbidity worldwide. The present study was undertaken to determine the number of term neonates and etiology with meningitis in clinically suspected cases of neonatal sepsis.

METHODS

Study design and participants

This is a prospective, observational hospital based study. Patients were eligible if they were term neonates with clinical sepsis admitted to limerick maternity hospital and either underwent a lumbar puncture or, if lumbar puncture was contraindicated, had clinically suspected meningitis and an appropriate pathogen identified either in blood culture or on blood PCR. Neonates with shock and severe cardio respiratory instability, major congenital malformations, LP was contraindicated were excluded.

Method of collection of data:

- The study period was from 01-01-2013 to 31-12-2013.
- Written informed consent was taken from the parents.
- Term neonates admitted to kent health alliance hospital University regional and maternity hospital limerick with "clinical sepsis"* were evaluated as per the structured proforma. They were evaluated clinically and a set of investigations in relation to sepsis done immediately and LP was performed under strict aseptic precautions for CSF analysis.

***Clinical features suggestive of sepsis and presence of one of the following Criteria,[13]**

a. Existence of predisposing factors: maternal fever or foul smelling liquor or prolonged rupture of membranes (>18 hrs.).

b. Positive septic screen: two of the four parameters namely, TLC <5000/mm3 or absolute neutrophil count<1800 / mm3, band to total polymorph ratio of > 0.2, C-reactive protein >1mg/dl and micro ESR>10 mm 1st hour.

c. Radiological evidences of pneumonia.

 Meningitis was diagnosed in neonates with clinical sepsis who met all of the following criteria on CSF analysis:

1. CSF cytology showing >30 cells with more than 60% polymorphs.
2. CSF glucose <50% of blood glucose (Blood glucose done simultaneously).
3. CSF protein >150 mg/dl.

DEFINITIONS:[13]

TERM-Gestational age of 37 to less than 42 completed weeks (i.e. 259 to 293 days).

NEONATAL PERIOD-It refers to the period of less than 28 days after birth.

LOW BIRTH WEIGHT (LBW) -Birth weight of less than 2500 gm.

PROLONGED RUPTURE OF MEMBRANES-Rupture of membranes or leaking for > 18 hours.

EARLY/ LATE ONSET SEPSIS

Early onset: Onset <72 hours.

Late onset: Onset >72 hours.

CLINICAL FEATURES SUGGESTIVE OF POSSIBLE SEPSIS/SEPTECEMIA

Lethargic or unconscious or less than normal movements or fast breathing (RR ≥60 breaths per minute) or severe chest in drawing or nasal flaring or grunting or feels hot to touch(axillary temperature ≥37.50c) or feels cold to touch(axillary temperature ≤35.50c) or bulging fontanel or ≥ 10 skin pustules.

The blood samples were collected under all aseptic precautions in NICU, in non-siliconized vacutainer tubes with tripotassium EDTA as an anticoagulant.

Another 2 ml was taken for conventional blood culture. Also 1 ml blood sample was taken for estimation of semi-quantitative CRP levels.

Total leukocyte count

Sysmex auto analyser was used to analyse the sample and counter checked. Leucopoenia with count less than 5000 cells/cu mm was considered as evidence of sepsis.

Differential count

Peripheral blood smears were prepared using smooth edged glass spreader resulting in tongue shaped smears, stained with Leishman stain and examined under oil immersion light microscopy at a final magnification of 1000. Differential counts were performed on Leishman stained smears and about 300 cells were counted.

Absolute neutrophil count of less than 1800 cells/cu mm was considered as evidence of sepsis. Likewise, immature: total neutrophil ratio of more than 0.2 was considered as a case of sepsis.

Micro- Erythrocyte Sedimentation Rate (Micro-ESR)

Micro-ESR of more than 10 mm at the end of 1 hour was considered significant. It was done by using pre-heparinised micro-haematocrit tube with internal diameter of 1.1 mm and total length of 75 mm. Tube was filled with capillary action.

Air was not allowed to interrupt the blood column. Lower end of tube was closed with plasticin and then tube was fitted vertically by means of sticking plaster. The fall of erythrocyte at the end of the hour was measured accurately to the nearest millimetre.

C - reactive protein (CRP)

The C - reactive protein was estimated semi-quantitatively by the latex slide agglutination method.

Principle: The latex slide agglutination test is based on the immunological reaction between CRP antigen and latex particles coated with mono-specific antihuman CRP antibody.

The kit consisted of a plastic slide with six reaction circles, sample dispensing pipettes, mixing sticks, rubber teats, CRP latex reagent, and positive and negative controls. Serum obtained from blood collected in plain bulb was used as test sample.

Method: Bring the serum samples and reagents to the room temperature. Using a plastic dropper, a drop of test serum was placed within the area on the glass slide.

One drop of latex CRP reagent was added to it, taking precaution that the dropper tip does not touch the liquid on the slide. Using mixing stick provided, the serum and CRP latex reagent is mixed and spread uniformly over the entire circle. Rock the slide gently back and forth. Look for macroscopic agglutination at exactly two minutes in a direct light source. Positive and negative controls are also run simultaneously.

Results were interpreted as follows: Agglutination seen macroscopically shows positive test indicative of a CRP concentration equal to or above 1 mg/ dl. Smooth suspension without any noticeable agglutination shows negative test indicative of a CRP concentration below 1 mg/dl.

Blood culture

A sample of 2cc of blood was collected in a conventional blood culture bulb using brain heart infusion as the transport media. It was incubated and grown on chocolate and Mc-Conkey media. On detection of growth of any organisms, it was reported in 3 days and was further incubated and sub cultured. Antibiotic sensitivity was detected appropriately. A report of no growth was given when there was no positive growth in any plates after a period of one week.

Lumbar puncture:

LP was done under aseptic precautions with neonate in lateral flexed position with neck extension to avoid hypoxemia. Three to five drops of CSF was collected in X- ray:

Asymmetry of reticulo-granular pattern with air bronchogram, coarse granular patchy infiltrates with irregular areas of hyperinflation were considered as radiological evidence of pneumonia.

Statistical analysis

All the findings were recorded and comparisons drawn between clinical profile, blood culture results, and the sepsis screen tests. Data was entered in Microsoft Excel 2015 and analysed using the SPSS software version 23.0(Statistical Package for the Social Sciences, IBM Inc. New York) and categorical tables, Chi-square values and the results correlated. Conclusions were drawn from the tabulated results. Test result is considered significant if *p* value is less than 0.05 (i.e. 5%). 3 separate sterile containers and sent for cytological, biochemical and microbiological analysis. If the LP was traumatic, the CSF sent for gram stain and culture and LP was repeated 24-48 hours later. Cytological and biochemical analysis were done within 30 minutes of drawing the sample.

CSF cytological analysis:

CSF was mixed with toluidine blue (2 or 3:1) and transferred to neubauer chamber using a pipet. Focussed and cells were counted in all 9 chambers under 40x magnification.

CSF biochemical analysis:

TRANSASIA XL-300 auto-analyser was used for CSF protein, chloride, glucose estimation and results were counter checked.

CSF microbiological analysis:

Two swabs soaked in CSF samples were prepared. One swab was used for smear preparation and gram staining. The second swab was used for inoculating on different media such as MacConkey agar, blood agar, chocolate agar, thoglycollate broth. Isolate further identified by relevant biochemical reactions as per the department protocol.

RESULTS

Depending on the age at presentation, cases were divided into early onset sepsis (<72 hours) and late onset sepsis (>72hours). Meningitis was present in 2(22.22%) early onset sepsis cases and 9(77.78%) late onset sepsis cases. The mean age was 5.58days (± 4.70) [Range 1-20 days]. Meningitis was common in late onset sepsis cases.

Meningitis was present in 5(55.56%) males and in 4(44.44%) females. Male: female ratio was1.25:1. Though, statistically not significant, males were more predisposed for sepsis as well as meningitis.

The mean birth weight was 2408gms±462. The maximum weight recorded was 3.66 kg and a minimum of 1.83 kg. Seven (77.78%) cases were small for gestational age babies, 2(22.22%) cases were normal birth weight babies. Meningitis was more common in small for gestational age babies. Inborn cases were 4(44.44%) in our study and 5(55.55%) cases were out born.

Two cases had history of fever in mother, while 5 cases had history of passage of foul liquor and 9 cases had history of PROM >18 hours. All these predisposing factors were present in early onset sepsis with meningitis cases.

CLINICAL MANIFESTATIONS IN MENINGITIS

Decreased feeding, lethargy were the common presenting complaints. Poor cry, activity, reflex, hypothermia was the common presenting signs.

LABORATORY FINDINGS IN MENINGITIS CASES

No meningitis cases had radiological evidences of pneumonia.

BLOOD & CSF CULTURE RESULTS IN MENINGITIS CASES

Blood culture was positive in 8(88.89%) neonates while it was negative in 1(11.11%) cases.

BASE LINE CHARACTERSTICS OF CLINICAL SEPSIS CASES (n=100)

Table 1: Base line characteristics of clinical sepsis cases

BASE LINE CHARACTERSTICS		NUMBER	PERCENTAGE	MEAN±SD
AGE DISTRIBUTION	<72 hours	64	64	5.85days±4.81
	>72 hours	36	36	
SEX DISTRIBUTION	MALE	42	42	-
	FEMALE	58	58	
BIRTH WEIGHT DISTRIBUTION	<2500gms	36	36	2586gms±462gms
	>2500gms	64	64	
ADMISSION CATEGORY	INBORN	43	43	-
	OUTBORN	57	57	
MATERNAL RISK FACTORS	FEVER	2	2	-
	FOUL	5	5	
	LIQUOR			
	PROM>18 hrs.	9	9	
BLOOD CULTURE	POSITIVE	17	17	-
	NEGATIVE	83	83	
CSF CULTURE	POSITIVE	6	6	-
	NEGATIVE	94	94	

A total of 9(9%) clinical sepsis cases were diagnosed to have meningitis based upon CSF cytological and biochemical criteria.

CLINICAL MANIFESTATIONS IN MENINGITIS CASES (n=9)

Table 2: Depiction of clinical manifestations: symptoms in meningitis cases.

SYMPTOMS	NUMBER (%)
Decreased feeding	7(77.77%)
Lethargy	6(66.67%)
Convulsions	4(44.44%)
Fever	2(22.22%)
Hurried breathing	1(11.11%)
Jaundice	1(11.11%)
Vomiting	1(11.11%)
SIGNS	
Poor cry, activity, reflex	6(66.67%)
Hypothermia	5(55.55%)
Tachycardia (HR>160bpm)	4(44.44%)
Prolonged CRT	2(22.22%)
Bulged AF	3(33.33%)
Tachypnea (RR>60)	2(22.22%)
Pustules	1(11.11%)
Icterus	1(11.11%)

LABORATORY FINDINGS IN MENINGITIS CASES (n=9)

Table 3: Statistical analysis of laboratory investigations

PARAMETERS	MEAN VALUE	RANGE
Hemoglobin	12.52gm%±0.92	11-14 gm%
TLC	8529/mm3±6305	3300-24,000/ mm^3
ANC	4578/mm3±4463	1,000-16,000/ mm^3
I:T ratio	0.17±0.06	0.09-0.33
micro ESR	15.94mm±2.24	13-19 mm
Platelet count	1,33,352/mm^3±62388	58,000-2,50,000/ mm^3

Table 4: Summary of meningitis cases (n=9)

BASE LINE CHARACTERSTICS		NUMBER	%	P Value
AGE DISTRIBUTION	<72 hours	2	22.22	0.003
	>72 hours	7	77.78	
SEX DISTRIBUTION	MALE	5	55.56	>0.05
	FEMALE	4	44.44	
BIRTH WEIGHT DISTRIBUTION	<2500gms	7	77.78	0.003
	>2500gms	2	22.22	
ADMISSION CATEGORY	INBORN	4	44.44	>0.05
	OUTBORN	5	55.56	
MATERNAL RISK FACTORS	PRESENT	2	22.22	0.003
	ABSENT	7	77.78	
BLOOD CULTURE	POSITIVE	8	88.89	-
	NEGATIVE	1	11.11	
CSF CULTURE	POSITIVE	3	33.33	-
	NEGATIVE	6	66.67	

DISCUSSION

Neonatal meningitis is the inflammation of the meninges typically occurring within the first 30 days of life. Despite the advancements in neonatal intensive care units and increased availability of antibacterial and supportive medications, neonatal meningitis is still a serious disease with high morbidity and mortality rates.[13] The present study was carried out to determine the current incidence of meningitis in term neonates with clinical sepsis.

CLINICAL PROFILE:

SEX:

In the present study, the incidence of meningitis was higher in males (55.56%) compared to females with a male: female ratio of 1.25:1, but it was not statistically significant. This observation was consistent with other studies as depicted in the below table.

Table 5: Comparative table on male female ratio

STUDIES	M:F
Hristeva L et al[9]	2.8:1
Khalessi N et al[14]	1.22:1
Fatma Kamoun et al[15]	1.75:1
Altayeb M H[16]	2.1:1
Klinger G et al[17]	1.3:1
Our study	1.25:1

Though the exact reason for this male preponderance is not known with certainty, it is probably due to the fact that the factors regulating the synthesis of globulins are situated on the X chromosome. Since the male has only one X chromosome, he is less immunologically protected than the females.[18]

WEIGHT:

In our study 77.78%of the meningitis cases were having weight less than 2500gms. The mean birth weight 2408gms±462 in our study. This observation was consistent with other studies as depicted in the below table.

Table 6: Comparative table on mean birth weight.

STUDIES	MEAN BIRTH WEIGHT LBW INCIDENCE
Hristeva L et al[9]	2091 gms
Kavuncuoglu S et al[19]	2480±924 g
Altayeb MH et al[16]	2229 gms
Nel E et al[20]	2320 gms
Our study	2480±462

Low birth weight is a factor associated most significantly with enhanced risk for bacterial sepsis and meningitis in neonates. This is because of immature defence mechanisms such as low levels of Ig G antibodies and inefficient cellular immunity. [21,22]

EARLY ONSET V/S LATE ONSET MENINGITIS:

Meningitis occurs due to haematogenous spread and is sequelae of bacteraemia. [23,24] As bacteraemia complications are common in late onset sepsis, and meningitis is frequent among late onset sepsis cases.[23]

In our study, late onset meningitis was diagnosed in 77.78% cases. This observation was consistent with other studies. Hristeva L et al[9] (65.21%), Kamoun F et al[15] (69.1%), Altayeb MH[16] (58%) and Chang C-J et al[25] (80%)

MATERNAL RISK FACTORS:

Presence of maternal risk factors like premature rupture of membranes, fever, and passage of foul liquor predisposes to early onset sepsis as well as meningitis in neonates.

Maternal risk factors were present in 22.22% meningitis cases, more common maternal risk factor being PROM>18 hours. All those risk factors were present in early onset meningitis cases. Our observation was consistent with studies by Hristeva L et al[9] reported out of 23 neonatal meningitis cases, 4(17.39%) cases had PROM >24 hrs and 5(21.73%) cases had maternal pyrexia. Kavuncuogluet S al[19] reported PROM was present in 12.5% of the EOM cases and Khalessi N et al[14] reported that PROM was involved in 12.5% of early onset meningitis cases.

CLINICAL MANIFESTATIONS:

The signs and symptoms of neonatal meningitis are not easy to distinguish from those of sepsis. The most common presenting symptoms are lethargy, feeding problems, instability of temperature regulation, vomiting, respiratory distress, and apnea. A bulging fontanel may be seen, but this is usually a late manifestation.

Seizures are frequently observed and can be caused by either direct central nervous system inflammation or by metabolic abnormalities.[26]

Decreased feeding (77.77% cases), lethargy (66.67% cases) were the common presenting complaints among meningitis cases in our study. Other symptoms being hypothermia (55.55% cases), convulsions (44.44% cases), fever (22.22% cases). Poor cry, activity, reflex (66.67% cases) and tachycardia (44.44% cases), bulged AF (33.33% cases) were the common signs.

Khalessi N et al[14] reported poor feeding (60% cases); seizures (55% cases) were the common manifestations. While bulging of fontanel was noticed in only 5% patients.

Kavuncuoglu S et al[19] reported fever (39%), poor clinical status (25%), and poor feeding (16%) as the most common clinical features observed.

Kamoun F et al[16] reported fever (69.1% cases), poor feeding (49.1% cases), and hypothermia (16.4% cases) as the common presenting manifestations.

Chang CJ et al[25] reported fever, disturbed consciousness, and seizures were the three most common manifestations in the patients, accounting for 88%, 38%, and 30% of all manifestations, respectively.

CSF CULTURE:

The bacterial epidemiology differs from one country to another and according to the age at onset. The bacteriological profile in developing countries is dominated by enterobacteria, where as in industrialised countries, GBS, E.coli, Listeria monocytogenes predominates.[15,26]

CSF culture was positive in 3(33.33%) meningitis cases.

Prior use of antibiotics before the performance of the LP, the delay in the transport of the CSF to the laboratory and the low density of bacteria in CSF could be some of the reasons for low CSF culture positivity rate.[15]

BLOOD CULTURE:

Although there is a close relationship between bacterial sepsis and meningitis, it has been estimated that 15% to 30% of the infants with CSF-proven meningitis have negative blood cultures.[27]

In our study, blood culture was positive in 88.89% of meningitis cases and in 11.11% cases blood culture was negative. Blood culture results were concordant in 35.29% meningitis cases.

Altayeb MH et al[16] reported 58% of blood culture positivity among CSF culture proven meningitis and all isolates had the same organisms as in the CSF.

Garges HP et al[28] reported that 96.8% of the patients with a positive CSF culture had a blood culture examination and 62% had a positive bacterial growth. The organisms isolated in CSF and blood cultures were discordant in only 3.5% of cases.

This may be related to an increased use of antibiotics that has been advocated to prevent group B streptococcal disease [29] or prior use of antibiotics before referral.

CSF CELL COUNT, GLUCOSE, PROTEIN LEVELS:

Bacterial cultures of CSF are definitive for meningitis diagnosis in the absence of pre-treatment. On the other hand, the interpretation of CSF cell counts and chemical analyses is difficult. The upper limit of the mean ±2 standard deviations. CSF cell count in term neonates is 25 cells/mm3, but white blood cell counts up to 32/mm3 may be found in uninfected neonates.[30]

We performed CSF culture in all clinically suspected sepsis cases. We could have included 5 more cases if our CSF cell criteria was >21/mm3.

Garges H P et al[28] reported highest sensitivity (97%) when the threshold was any presence of WBCs in the CSF, but this also led to the lowest specificity (11%) for meningitis diagnosis in their study. Using 21 WBCs as the upper limit of the threshold led to a sensitivity of 79% and a specificity of 81%.

In this regard it may become essential to conduct some more multi centric studies to revise the cytological criteria for diagnosis of meningitis.

CONCLUSION

- Meningitis was present in 9% clinical sepsis cases.
- Meningitis was common in late onset sepsis (77.78%) cases.
- Neonatal meningitis was more common in small for date babies (70.58% cases).
- Blood culture was positive in 88.89% cases. CSF culture grown organisms in 35.29% cases.

More multi-centric studies are required to revise the CSF cytological criteria to diagnose meningitis.

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