Original Article

Access this article online

Quick Response Code:

Website: www.jacmjournal.org

DOI: 10.4103/jacm.jacm_19_17

Aetiology of acute pyogenic meningitis in children in a tertiary care hospital, Kerala

KM Rafeeda, Beena Paul[1], Lizy Mathew[2]

Abstract:

INTRODUCTION: Acute bacterial meningitis is a medical emergency, and the diagnosis is by culture of cerebrospinal fluid (CSF). In this study, we looked at the changing aetiology of acute pyogenic meningitis in the context of the availability of several vaccines.

MATERIALS AND METHODS: The aim of this study was to find out the aetiology and antibiotic susceptibility pattern of acute pyogenic meningitis in children between one month and 12 years in one year in a tertiary care centre. A cross-sectional study was conducted in the Department of Microbiology, Medical College Hospital, Trivandrum, in collaboration with Department of Paediatrics, SATH, Trivandrum and Christian Medical College, Vellore. CSF samples were processed by doing Gram-staining and culture in appropriate media. Latex agglutination test (LAT) and PCR were done in all cases for the primary pathogens. Blood culture and sensitivity were also done for all patients.

RESULTS: *Streptococcus pneumoniae* (62.5%) was the most common aetiological agent for acute bacterial meningitis followed by *Klebsiella pneumoniae* subspp *pneumoniae*, Group B haemolytic Streptococci and *Elizabethkingia meningosepticum*. LAT could pick up one culture negative case of pneumococcal meningitis. Blood culture was positive in 37.5% of CSF culture positive cases.

Keywords:

Acute bacterial meningitis, antibiotic susceptibility pattern, cerebrospinal fluid, *Elizabethkingia meningosepticum*, Group B haemolytic Streptococci, *Klebsiella pneumoniae* subspp pneumoniae, *Streptococcus pneumoniae*

Introduction

Meningitis, also termed leptomeningitis, is an inflammation of the membranes that surround the brain and spinal cord, thereby involving the arachnoid, the pia mater and the interposed cerebrospinal fluid (CSF). The three primary bacterial pathogens are *Neisseria meningitidis, Streptococcus pneumoniae* and *Haemophilus influenzae* Type b. Laboratory diagnosis is by the culture of CSF and blood. The mortality from bacterial meningitis is close to 100% in untreated individuals and is still up to 40% in those children who receive appropriate antibiotic treatment in developing countries.[1]

Department of Microbiology, Travancore Medical College, Kollam, [1]Priyadarshini Institute of Paramedical Sciences, [2]Department of Microbiology, Government Medical College, Trivandrum, Kerala, India

Address for correspondence:
Dr. KM Rafeeda, Travancore Medical College, Kollam, Kerala, India.
E-mail: rafeedakm@gmail.com

Paediatric bacterial meningitis is a neurological emergency which, in spite of advances in medical management, has a significant morbidity and mortality. Over recent decades introduction of new vaccines have led to a change in epidemiology of the disease; however, it remains a condition that requires a high index of suspicion, prompt diagnosis and early management.

Aim

The aim of this study was to find out the aetiology and antibiotic susceptibility pattern of acute pyogenic meningitis in children between one month and 12 years.

Objectives

1. To determine the aetiology of acute bacterial meningitis in children between

How to cite this article: Rafeeda MK, Paul B, Mathew L. Aetiology of acute pyogenic meningitis in children in a tertiary care hospital, Kerala. J Acad Clin Microbiol 2018;20:22-7.

one month and 12 years and antibiotic susceptibility pattern of the isolates
2. To determine the predictive accuracy of the various diagnostic tests done for bacterial meningitis such as antigen detection by latex agglutination test (LAT) and culture with polymerase chain reaction (PCR)
3. To determine the agreement between the CSF cultures and blood cultures in diagnosing acute pyogenic meningitis.

Materials and Methods

It was a cross-sectional study conducted in the Department of Microbiology, Medical College, Trivandrum, Department of Pediatrics, Sree Avittom Thirunal Hospital, Trivandrum, over a period of one year from June 2013 to May 2014. The samples for PCR were sent to Christian Medical College, Vellore by post and the results were received by E-mail diagnostic facility was not there in Trivandrum Medical College.

Study population

Infants and children from one month to 12 years of age admitted with signs and symptoms of pyogenic meningitis in Sree Avittom Thirunal Hospital, Trivandrum.

Inclusion criteria

Children between one month to 12 years of age with signs and symptoms of acute meningitis such as fever, headache, neck stiffness, vomiting, irritability, drowsiness, bulging fontanelle, positive Kernig's sign and Brudzinki sign.

Exclusion criteria

- Cerebral abscesses.
- Postoperative cases and shunt meningitis
- Neonates (till 30 days of birth).

Sample collection and processing

The samples of CSF were collected by lumbar puncture by an expert paediatrician under aseptic conditions and transported in sterile dry bottles with an average volume of 1–5 ml. The samples were processed immediately.

Macroscopic examination, cell count, Gram-staining, culture on Blood Agar, Chocolate agar, Mac Conkey Agar and Glucose broth were done. LAT was done using BD Directigen™ Meningitis Combo Test kit. Samples for PCR were sent to CMC Vellore for the primary pathogens. Real-time PCR was done based on the laboratory diagnosis manual of CDC, chapter 10 in Vellore and the results were received by E-mail. Blood culture was also performed by conventional method.

Results

As per the inclusion and exclusion criteria 651 patients (males 427 and females 224) with signs and symptoms of acute bacterial meningitis participated in the study. Bacterial aetiology was identified in 6 males (1.4%) and 2 females (0.89%).

Maximum number of suspected cases were in the age group six months to one year, number 160 (25%) followed by 1–2 years, number 141 (22%) [Table 1].

Of the 651 samples processed only eight were due to bacterial pathogens.

Most of the cases were in one to six months old infants, but *S. pneumoniae* was found to be more common in older children [Table 2].

Blood culture was positive in 37.5% of CSF culture positive cases [Table 3].

LAT could identify one case of culture-negative pneumococcal meningitis. False-positive latex results were obtained for *H. influenzae, N. meningitidis* and Group B *Streptococci* [Table 4].

All the Gram-positive isolates were sensitive to the antibiotics and MIC values were found out and compared by E test for Penicillin and Ceftriaxone in case of pneumococci [Table 5].

The mortality rate of acute bacterial meningitis in the study was 33.3%. Only two cases of pneumococcal meningitis succumbed to the infection. All others recovered.

In the present study, the complications that developed were one case each of hydrocephalus and temporal lobe abscess.

Treatment followed: Meningitis caused by pneumococci and *Klebsiella pneumoniae* were treated by giving Ceftriaxone. Group B Streptococcal meningitis was treated with Crystalline Penicillin. *Elizabethkingia meningosepticum* meningitis was treated with Co-trimoxazole.

Discussion

In spite of the availability of antibiotics and the introduction of vaccines for immunoprophylaxis, bacterial meningitis remains a common disease worldwide, with high morbidity and mortality and the choice of initial antimicrobial therapy is based on the most common pathogen prevalent in a particular geographical area, age group and its antibiotic sensitivity pattern.

In the present study, 427 (65.6%) samples were of males and 224 (34.4%) samples were of females. Six isolates from males and two isolates from females were obtained. Most of the patients in the present study had fever (86%), headache (63%), vomiting (47%), neck stiffness (47%) and upper respiratory tract infection (38%). Fever was the presenting symptom in 86% of cases Surinder *et al*., in his study done at Maulana Azad Medical College, New Delhi in 2007 had reported that fever was present in 81.5% cases.[2] Hence, the current study is also in concordance with the above study.

Most of the patients in the current study were in the age group of six months to one year, and the positive cases were in the age group of one month to six months. A study conducted by Schuchat *et al*. in 1995 showed that two-thirds of patients with bacterial meningitis were between one month and five years of age.[3]

In the present study, *S. pneumoniae* was the major pathogen (62.5%). Mani *et al*. have reported 61.8% cases of pneumococcal meningitis in South India over a 10-year retrospective study from 1996 to 2005 which is comparable with the present study.[4]

Schuchat *et al*. reported 46% pneumococcal meningitis cases during 1995 in the United States.[3] Jones *et al*. reported a rate of 11% for *S. pneumoniae* in CSF samples of meningitis patients in the US from 2000 to 2002.[5] The reason for this difference may be due to vaccination programs.

A study conducted by Durand *et al*. in the US from 1962 to 1988 on acute bacterial meningitis also showed that the most common pathogen is *S. pneumoniae*.[6]

India has not yet taken up routine pneumococcal vaccination in the primary immunisation program of infants and children. That might be the reason for the high incidence of pneumococcal meningitis in most of the studies including current study. There are certain challenges for the introduction of the vaccine in India. There is lack of current data from India to show change in serotype prevalence over time and there is a lack of typing facilities in most of the laboratories. A review published in Vaccine in 2009 also highlights the lack of large, sustained long duration studies to estimate the incidence of actual disease burden.[7]

Pneumococcal vaccines which have proved to be beneficial in developed countries need further studies to prove its efficacy in the developing countries by incorporating prevalent serotypes. In the current study also, serotyping was not done. Hence, in future, the seroprevalence in India has to be assessed, and the vaccination has to be included in routine immunisation schedule. Now Indian Association of Pediatrics recommend pneumococcal vaccination as an optional vaccine in their schedule.

H. influenzae Type b which is also a primary pathogen was not obtained in the current study period. Before the introduction of the conjugate Hib vaccine in the 1980s, Hib alone accounted for approximately half of the cases of meningitis in infants. Following vaccination, 78% reduction was observed.[8] Literature states that with the routine use of conjugated vaccines against the Type b strain in many countries, the disease by this organism has almost disappeared.[9] In Kerala Pentavalent vaccination was introduced under National Program of immunisation in 2011, so most of the children in the current study were immunised.

Neisseria meningitidis, a primary pathogen was not isolated in children in the present study. The organism was isolated in many adults during the study period. The global patterns of meningitis and sepsis caused by meningococci are more diverse, because of its greater epidemic potential.[10]

In the current study, 50% of proven bacterial meningitis (4 out of 8) were in the age group of one month to six months. The agents identified were Group B Streptococci *Klebsiella pneumoniae* subspp *pneumoniae, Elizabethkingia meningoseptica* and *S. pneumoniae*. In the neonatal period, premature and term babies up to three months of life, Group B Streptococci is the predominant pathogen in many developed countries.[11] Coliform bacilli are the second most common cause. Group B *Streptococcus* was isolated in a 34-day-old term neonate in the present study which was sensitive to the first line antibiotics. It was a case of late-onset disease. It has been shown that even in postneonatal period, it should be considered as an important pathogen.

In the current study Klebsiella pneumoniae subspp pneumoniae, Elizabethkingia meningoseptica and Group B Streptococci were isolated in age group of one to six months. These are the usual bacterial pathogens causing neonatal meningitis. *Listera monocytogenes* is occasionally responsible for bacterial meningitis in this age group, usually as zoonotic outbreaks. However, in the current study, *Listeria* was not isolated. Thigpen *et al*. in a study done in the United States in 2011 concluded that the incidence of Listeria meningitis increases with age in adults, especially after age 50, probably due to immune senescence or decreased immunity with age.[12]

A study conducted by Tang *et al*. in Taiwan had shown that there was an increased prevalence rate of Klebsiella meningitis after 1986.[13] The predominant one is *Klebsiella pneumoniae* (48.5%) followed by *Klebsiella oxytoca* (10%)

and *Klebsiella ozaenae* (3%).In the current study *Klebsiella pneumoniae subspp pneumoniae* accounted for 12.5% cases of meningitis. He was a 32-day-old child who later developed hydrocephalus. Initially, extraventricular drainage and later ventriculoperitoneal shunt was performed.

Elizabethkingia meningoseptica which was resistant to Ampicillin and Cephalexin was isolated from an infant of 35 days old in the present study. It is one of the causes for neonatal meningitis. In a study conducted by Hsu *et al*. in Taiwan concluded that the incidence of *Elizabethkingia meningoseptica* bacteraemia has increased from 7.5 in 1996–35.6 in 2006. More than 80% of isolates in that study were sensitive to Trimethoprim-Sulfamethoxazole.[14]

In the present study, LAT for the detection of antigen of *S. pneumoniae, Neisseria meningitidis, H. influenzae* Type b, Group B Streptococci and *Escherichia coli* were performed in all the samples, the test was positive in 11 out of 651, culture was positive in five cases and real-time PCR was positive in six cases. One culture negative and PCR positive case were Pneumococcal meningitis. Gram-stain and the LAT were able to detect that case. Moreover, the remaining five latex positive cases were *H. influenzae* Type b (2 cases), *Neisseria meningitidis* C/W 135 (2 cases) and Group B *Streptococcus* (1 case). All those patients had deranged CSF sugar, protein and cell count and were treated as pyogenic meningitis.

In a study conducted by Syeda Fasiha Mohammad *et al*. on diagnostic value of LAT on bacterial meningitis, they reached the conclusion that sensitivity, specificity, positive predictive value and negative predictive value of Gram-stain are 53.33%, 83.52%, 36.36% and 91.02%, respectively. LAT had a sensitivity of 66.66%, specificity of 87.91%, positive predictive value of 35.29% and negative predictive value of 96.38%. As the number of positive cases in the present study was very less, further statistical analysis to find out the above-said values could not be performed.

No test can replace the utility of culture especially so in neonates as LAT does not identify Enterobacteriaceae other than *E. coli*. Thus, CSF culture is crucial to the diagnosis of neonatal meningitis regardless of the other laboratory results. Despite its drawbacks, LAT is considered to be simple, rapid procedure suitable to be used as an adjunct laboratory test. It was also found to be valuable in detecting fastidious bacteria that are difficult to isolate on culture. However, it should not be used indiscriminately as a screening tool in the routine diagnostic laboratory, and its use should be reserved for the detection of bacterial antigens in CSF specimens that fail to reveal the organism on Gram-stain.

Table 1: Distribution of cases according to age

Age	*n* (%)
1-6 months	115 (18)
6 months to 1 year	160 (25)
1-2 years	141 (22)
2-3 years	68 (10)
3-4 years	20 (3)
4-5 years	26 (4)
5-6 years	19 (3)
6-12 years	102 (16)

Table 2: Relative frequency of bacterial pathogens in relation with age

Organism	1-6 months	6 months to 2 years	2-4 years	4-6 years	6-12 years
Streptococcus pneumoniae	1	0	1	0	3
Group B Streptococci	1	0	0	0	0
Klebsiella pneumoniae sub spp. *pneumoniae*	1	0	0	0	0
Elizabethkingia meningoseptica	1	0	0	0	0
Total number	4	0	1	0	3

Table 3: Correlation between cerebrospinal fluid and blood culture positivity

Organism	CSF culture positive	Blood culture positive
Streptococcus pneumoniae	4	2
Group B Streptococci	1	1
Klebsiella pneumoniae	1	0
Elizabethkingia meningoseptica	1	0
Total	7	3

CSF: Cerebrospinal fluid

Table 4: Analysis of aetiological agents in cerebrospinal fluid by various diagnostic methods

Organism	Gram stain	Latex	Culture	PCR
Pneumococci	6	6	5	6
Group B Streptococci	2	2	1	1
Neisseria meningitidis	0	2	0	0
Haemophilus influenzae	0	2	0	0
Klebsiella pneumoniae	1	0	1	1
Elizabethkingia meningoseptica	1	0	1	1
Total	10	12	8	9

PCR: Polymerase chain reaction

In the present study, two patients expired. The mortality rate was 25%. Both the cases were due to *S. pneumoniae*. Studies have shown that the mortality rate of acute bacterial meningitis is 20 to 34 % and the most common agent causing mortality is Streptococcus *pneumoniae*.[2,3]

Pneumococcal isolates in the present study were uniformly sensitive to Penicillin as detected by disc diffusion method (Oxacillin 1 μg) and MIC detection by E test (Himedia). A study done by Kragsbjerg

Table 5: Analysis of sensitivity pattern of Gram-positive cocci

Drug	*Streptococcus pneumoniae* (%)	Group B Streptococci (%)
Penicillin	5 (100)	1 (100)
Oxacillin	5 (100)	Not tested
Ampicillin	Not tested	1 (100)
Ceftriaxone	5 (100)	1 (100)
Erythromycin	Not tested	1 (100)
Vancomycin	5 (100)	1 (100)
Meropenem	5 (100)	Not tested
Chloramphenicol	5 (100)	1 (100)

Table 6: Analysis of sensitivity pattern of Gram-negative bacilli

Drug	*Klebsiella pneumonia* sub spp. *pneumoniae* (%)	*Elizabethkingia meningoseptica* (%)
Ampicillin	0	0
Cephalothin	1 (100)	0
Gentamicin	1 (100)	0
Ciprofloxacin	1 (100)	1 (100)
Amikacin	1 (100)	1 (100)
Ceftriaxone	1 (100)	1 (100)
Trimethoprim-sulfamethoxazole	1 (100)	1 (100)
Vancomycin	Not tested	1 (100)
Meropenem	1 (100)	1 (100)
Chloramphenicol	1 (100)	1 (100)

et al.[15] in 1994 also recorded that all pneumococcal isolates were fully sensitive to penicillin in his study. Recently, Penicillin resistance is increasing in case of pneumococci. In Spain, 43% of pneumococci were resistant to Penicillin. In one study conducted by Fenoll *et al.* reported a case of meningitis due to mixed infection with Penicillin-resistant and susceptible strains of *S. pneumoniae*.[16]

Meningitis caused by pneumococci and *Klebsiella pneumoniae* were treated by giving Ceftriaxone. Group B Streptococcal meningitis was treated with Crystalline Penicillin. *E. meningosepticum* meningitis was treated with Co-trimoxazole.

Conclusion

S. pneumoniae remains the most common pathogen (62.5%) of acute bacterial meningitis in children followed by Group B *Streptococci*, *Klebsiella pneumonia* subspp pneumonia and *Elizabethkingia meningoseptica*. The study highlights the importance of vaccination to prevent the disease. Identification of serotype is very essential for vaccination strategy, which was not done in the present study and it is suggested that further studies on molecular epidemiology of pneumococcal meningitis would be beneficial for implementation of vaccination.

Widespread use of *H. influenzae* Type b conjugate vaccines has drastically reduced the threat of bacterial meningitis in children from one month to five years of age.

The study could demonstrate the high diagnostic value of bacterial antigen detection by LAT in situations where the patient had received antibiotic treatment Blood culture was positive in 37.5% of CSF culture positive cases which shows the importance of sending a blood culture if at all the patient has increased intracranial pressure or some other contraindication for lumbar puncture.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global burden of disease study. Lancet 1997;349:1269-76.
2. Surinder K, Bineeta K, Megha M. Latex particle agglutination test as an adjunct to the diagnosis of bacterial meningitis. Indian J Med Microbiol 2007;25:395-7.
3. Schuchat A, Robinson K, Wenger JD, Harrison LH, Farley M, Reingold AL, *et al.* Bacterial meningitis in the United States in 1995. Active surveillance team. N Engl J Med 1997;337:970-6.
4. Mani R, Pradhan S, Nagarathna S, Wasiulla R, Chandramuki A. Bacteriological profile of community acquired acute bacterial meningitis: A ten-year retrospective study in a tertiary neurocare centre in South India. Indian J Med Microbiol 2007;25:108-14.
5. Jones ME, Draghi DC, Karlowsky JA, Sahm DF, Bradley JS. Prevalence of antimicrobial resistance in bacteria isolated from central nervous system specimens as reported by U.S. hospital laboratories from 2000 to 2002. Ann Clin Microbiol Antimicrob 2004;3:3.
6. Durand ML, Calderwood SB, Weber DJ, Miller SI, Southwick FS, Caviness VS Jr., *et al.* Acute bacterial meningitis in adults. A review of 493 episodes. N Engl J Med 1993;328:21-8.
7. Bravo LC; Asian Strategic Alliance for Pneumococcal Disease Prevention (ASAP) Working Group. Overview of the disease burden of invasive pneumococcal disease in Asia. Vaccine 2009;27:7282-91.
8. Peltola H. Worldwide *Haemophilus influenzae* type b disease at the beginning of the 21st century: Global analysis of the disease burden 25 years after the use of the polysaccharide vaccine and a decade after the advent of conjugates. Clin Microbiol Rev 2000;13:302-17.
9. Centers for Disease Control and Prevention (CDC). Progress toward elimination of *Haemophilus influenzae* type b invasive disease among infants and children – United States, 1998-2000. MMWR Morb Mortal Wkly Rep 2002;51:234-7.
10. Stephens DS, Greenwood B, Brandtzaeg P. Epidemic meningitis, meningococcaemia, and *Neisseria meningitidis*. Lancet 2007;369:2196-210.
11. Sáez-Llorens X, McCracken GH Jr. Antimicrobial and anti-inflammatory treatment of bacterial meningitis. Infect Dis

Clin North Am 1999;13:619-36, vii.

12. Thigpen MC, Whitney CG, Messonnier NE, Zell ER, Lynfield R, Hadler JL, *et al*. Bacterial meningitis in the United States, 1998-2007. N Engl J Med 2011;364:2016-25.
13. Tang LM, Chen ST, Hsu WC, Chen CM. Klebsiella meningitis in Taiwan: An overview. Epidemiol Infect 1997;119:135-42.
14. Hsu MS, Liao CH, Huang YT, Liu CY, Yang CJ, Kao KL, *et al.* Clinical features, antimicrobial susceptibilities, and outcomes of *Elizabethkingia meningoseptica* (*Chryseobacterium meningosepticum*) bacteremia at a medical center in Taiwan, 1999-2006. Eur J Clin Microbiol Infect Dis 2011;30:1271-8.
15. Kallman KP, Olcen J. Pneumococcal meningitis in adults. Scand J Infect Dis 1994;26:659-66.
16. Fenoll A, Jado I, Vicioso D, Pérez A, Casal J. Evolution of *Streptococcus pneumoniae* serotypes and antibiotic resistance in Spain: Update (1990 to 1996). J Clin Microbiol 1998;36:3447-54.