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Clinical Profile and Bacterial Etiology of Acute Pyogenic Meningitis in Children

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The purpose of this study was to study clinical profile and bacterial etiology of acute pyogenic meningitis (APM) in children. This study was hospital-based, cross-sectional, descriptive study conducted among children of 0-12 years old with pyrexia less than one week and clinically suspected APM cases, admitted to Yankin Children's Hospital and Thingangyun Sanpya General Hospital from January to December, 2013. Out of 103 total cases, 44 (42.7%) cases had abnormalities in cerebrospinal fluid (CSF) examination (CSF pleocytosis, reduced CSF glucose concentration less than 40 mg/dl and increased CSF protein concentration more than 45 mg/dl). Among those 44 cases, most of the children presented with fever (90.9%) and convulsion (59.1%). Signs of meningism such as neck stiffness (31.8%), Kernig's sign (18.2%) and Brudzinski's sign (11.3%) were detected. There were 11 cases (25%) having acute complication and 4 cases of death (9%). Among those 44 cases, 12 (27.2%) cases were confirmed by detecting bacteria in blood or CSF culture. *Staphylococcus aureus* (33.3%), *Neisseria meningitidis* (16.6%), *Escherichia coli* (16.6%), *Streptococcus pneumoniae* (8.3%), *Enterococcus faecalis* (8.3%), *Streptococcus viridians* (8.3%) and *Listeria monocytogenes* (8.3%) were isolated and most of the isolated bacteria were resistant to currently using empirical antibiotics, in which 11 culture-positive cases (91.6%) were resistant to cefotaxime and 10 culture-positive cases (83.3%) were resistant to ceftriaxone. Periodic review of causal organisms of APM and their antimicrobial spectrum are important to rationalize prescribing of antimicrobial agent.

Key words: Clinical profile and bacterial etiology, Acute pyogenic meningitis, Children

INTRODUCTION

Acute pyogenic meningitis (APM) is a medical emergency which warrants early diagnosis and aggressive therapy. Prior to the introduction of antibiotics in the 1940s, case fatality rate for epidemic and endemic pyogenic meningitis exceeded 70%. Since then, antibiotic use has reduced case fatality rates of APM to 25% or less.[1]

If meningitis is suspected, the diagnosis should be confirmed by examination of cerebrospinal fluid (CSF). However, it is usual practice to start empirical antibiotic therapy before the complete laboratory result is available. Such blind prescription requires knowledge of the most frequent etiological agents of meningitis in the local population.

Inability to choose appropriate antibiotics based on organisms isolated or its drugs sensitivity makes unnecessary prolongation of therapy, poor clinical response and increased complications. As variation of

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time, geography, patient's age and immunization programme, periodic review of APM in Myanmar is important to get accurate information regarding bacterial etiology.

MATERIALS AND METHODS

This study was hospital-based, cross-sectional, descriptive study conducted among children of 0-12 years old who had pyrexia less than one week and clinically suspected acute pyogenic meningitis cases, admitted to Yankin Children's Hospital and Thingangyun Sanpya General Hospital from January to December, 2013. They were examined according to proforma. History, clinical features and acute complications during hospital stay were recorded.

If there was no contraindication for lumber puncture, 2 ml of CSF and 1 ml of blood were collected under aseptic condition after receiving the written consent. One milliliter of CSF was sent for routine examination to Biochemistry Section, Clinical Pathology, National Health Laboratory. One milliliter of CSF was sent for Gram's stain, Ziehl-Neelsen stain, culture and sensitivity and inoculated blood culture bottle was sent for culture and sensitivity to Bacteriology Research Division, Department of Medical Research within three hours of sample collection.

Cerebrospinal fluid culture

After CSF was centrifuged at 2,000 rpm x 5 minutes, two drops of pellet were inoculated onto blood agar plate, MacConkey agar plate, nutrient agar plate and chocolate agar plate for isolation of bacterial pathogens. Inoculated blood agar plate and chocolate agar plate were incubated in 5%-10% CO_2 containing incubator. Isolated bacterial pathogen was identified by biochemical tests and proceeded to antibiotic susceptibility testing.

Blood culture

The inoculated blood culture bottles, containing 10 ml of trytose phosphate broth with 0.025% polyanetholsulfonate (liquid), were incubated aerobically at 37ºC and examined daily up to 7 days for visible growth. If visible growth was seen, a small amount of broth with a sterile loop was inoculated onto blood agar plate and MacConkey agar plate and incubated at 37ºC. If there was no visible growth on the first day, they were examined daily up to 7 days.

On the seventh day, the culture broth was subcultured onto blood agar plate, MacConkey agar plate, nutrient agar plate and chocolate agar plate and then incubated at 37ºC overnight. If culture and subculture were negative, it was reported as "No growth after 7 days incubation".

Antibiotic susceptibility testing

The antimicrobial susceptibility testing was performed by modified Kirby Bauer's disc diffusion method on Mueller Hinton agar (Beckton-Dickinson, USA). For disc diffusion test, commercially available discs (Oxoid Limited, England) such as penicillin (10 IU), ampicillin (10 µg), flucloxacillin-amoxacillin (10 µg), oxacillin (1 µg), piperacillin-tazobactum (100+10 µg), ciprofloxacin (5 µg), ceftriazone (30 µg), ceftazidine (30 µg), cefotaxime (30 µg), cefoperazone-sulbactum (75 µg), amikacin (30 µg), gentamicin (10 µg), cefotaxime (30 µg), choloramphenicol (30 µg) and vancomycin (30 µg) were used. *Escherichia coli* ATCC 25922 strain was used as quality control strain.

Zones of inhibition obtained were measured. Based on the zone size diameter according to the guidelines of Clinical Laboratory and Standard Institute (CLSI, 2012), the isolate was interpreted as susceptible, intermediate and resistant. In this study, the defining criterion for multiple drug resistance (MDR) was resistance to $\geq$3 of the antimicrobial agents belonging to different structural classes.

Data management

Demographic characteristics, clinical profile, microbiological spectrum and antibiotic sensitivity pattern of study group were analyzed. Data analysis was done using SPSS version 15.0.

Ethical clearance

This paper was done after getting approval from Institutional Ethical Review Committee of University of Medicine 2, Yangon.

RESULTS

Total 103 children were studied who were among children of 0-12 years old with pyrexia less than one week and clinically suspected APM cases. Among them, 44 (42.7%) cases had abnormalities in cerebrospinal fluid (CSF) examination (CSF pleocytosis, reduced CSF glucose concentration less than 40 mg/dl and increased CSF protein concentration more than 45 mg/dl).

Characteristics of study population

Among 44 clinically suspected acute pyogenic meningitis cases, the commonest age group was between two months and one year (14, 31.8%) and male was slightly predominant than female (1.09:1) **(**Table 1).

Table 1. Age and sex distribution in clinically suspected acute pyogenic meningitis cases

Age	Male	Female	Total (n=44)	Percent
0-<2m	4	4	8	18.2
2m-<1y	8	6	14	31.8
1y-<5y	6	3	9	20.5
≥5y	5	8	13	29.5
Total	23	21	44	

m=month, y=year

CSF abnormalities in clinically suspected acute pyogenic meningitis cases

Among 44 children, 31 children (70.4%) had only one CSF abnormality. Two CSF abnormalities were found in 10 children (22.7%). All CSF abnormalities were seen in three children (6.8%).

Clinical profile

Most of the children presented with fever (90.9%) and convulsion (59.1%). Signs of meningism such as neck stiffness (31.8%), Kernig's sign (18.2%) and Brudzinski's sign (11.3%) were detected (Table 2).

Table 2. Age group and presenting features in clinically suspected acute pyogenic meningitis cases

Presenting features	Age group				Total (n=44)	%
	0-<2m	2m-<1y	1y-<5y	≥5y		
Fever	7	12	9	12	40	90.9
Impaired conscious	0	3	2	6	11	25
Irritability	1	1	3	5	10	22.7
Headache	0	0	1	5	6	13.6
Convulsion	7	11	4	4	26	59.1
Bulging and tense AF	2	0	0	0	2	4.5
Cough	0	4	1	0	5	11.4
Apnea	0	0	1	0	1	2.3
Rapid breathing	1	2	1	0	4	9.1
Respiratory distress	2	3	1	0	6	13.6
Poor feeding	1	2	1	2	6	13.6
Nausea/vomiting	1	4	3	0	8	18.2
Loose motion	0	4	3	0	7	15.9
Neck stiffness	1	2	4	7	14	31.8
Kernig's sign	1	2	2	3	8	18.2
Brudzinski's sign	0	0	1	4	5	11.3

m=month, y=year

Distribution between causal organism and acute complications

Table 3. Distribution between causal organism and acute complications

Acute complication	A	B	C	D	E	Total (n=11)
Persistent fever	1	1	-	-	4	6
Quadriplegia/quadriparesis	1	1	1	-	3	6
Hemiplegia /hemiparesis	-	-	-	-	1	1
Cranial nerve palsy	-	-	-	-	2	2
Aphasia	-	-	-	1	2	3
SIADH	-	-	-	-	1	1
Expired	-	-	-	1	3	4

A=*Staphylococcus aureus,* B=*Streptococcus pneumoniae,* C=*Neisseria meningitidis,* D=*E. coli,* E=Blood and CSF Culture negative, SIADH=*Syndrome of inappropriate antidiuretic hormone Secretion*

Table 3 shows that there were 11 cases (25%) having acute complications and 4 cases of death (9%). Two expired cases were from 2 months to 1 year age group. Among 12 culture-positive cases, 5 children

had acute complications. Six children also had acute complications among 32 culture-negative cases.

Bacterial etiology

Among those 44 cases, 12 cases were confirmed by detecting bacteria in blood or CSF culture. Two cases had culture positive in both blood and CSF. There were 6 culture-positive cases in CSF only and 4 culture-positive cases in blood only. *Staphylococcus aureus* (33.3%), *Neisseria meningitidis* (16.6%), *Escherichia coli* (16.6%), *Streptococcus pneumoniae* (8.3%), *Enterococcus faecalis* (8.3%), *Streptococcus viridians* (8.3%) and *Listeria monocytogenes* (8.3%) were isolated.

DISCUSSION

Incidence of APM in this study (27.2%) is similar to other studies such as 24.2% in the study of Mandalay Children's Hospital[2] and 28.2% in the study of Salihat Sudan.[3]

Among 44 children with abnormalities of cerebrospinal fluid (CSF) examination, 31.8% belonged to two months to one year age group. Similarly, the greatest risk (40%) was found in one month to one year age group in the study done at North Okkalapa General Hospital and Yangon Children's Hospital in 1998.[4] Half of the incidence of APM among children in Romania also occurred in children under one year age.[5] Therefore, the greatest risk was found in two months to one year age group. The ratio of male and female was 1.09:1 in this study. There was no significant difference between male and female like some studies: M:F=1.08:1 in Myanmar study, 1998[4] and M:F=1.2:1 in Libyan Arab, 1998.[1]

CSF pleocytosis was detected in 38% of children. Among them, 76.5% had total cell count less than 50/mm^3 and 64.7% had polymorph dominance. This study had lower total cell count compared with two studies of Myanmar.[4, 6] Increased level of protein in CSF was detected in 77% of children. Among them, more than 100 mg% in CSF was detected in 64.7% of children. Protein level was as similar as other studies: 66% had more than 100 mg%[4] and 59% had more than 100 mg% in CSF at YCH, 1995.[6] Reduced level of sugar in CSF was detected in 13% of children, mean CSF glucose was 16.8 mg% with the range 1-65 mg%. In contrast to this study, mean CSF glucose was 17.8 mg% with the range 0-69 mg% in a study at YCH, 1982.[7]

In this study, the commonest presenting features were fever (90.9%) and convulsion (59.1%). Fever (98.38%) and seizures (70.96%) were the common features in the study of San Thanda, 2010.[2] Signs of meningism such as neck stiffness (31.8%), Kernig's sign (18.2%) and Brudzinski's sign (11.3%) were detected in this study. Neck stiffness (59.52%) and positive Kernig's sign (44.05%) were noted in the study done at YCH, 1999.[8] Neck stiffness (100%), positive Kernig's sign (90.9%) and Brudinski (59%) were noted in the study done in Sudan, 2010.[3] Incidence of meningism in this study was less than those of other studies done by Kyi Kyi Shwe, 1999[8] and Salih, *et al*.[3] because presenting features under one year were non-specific in this study.

APM was confirmed in 27.2% of cases by detecting bacteria in blood or CSF culture in this study. *Staphylococcus aureus* (33.3%), *Neisseria meningitidis* (16.6%), *Escherichia coli* (16.6%), *Streptococcus pneumoniae* (8.3%), *Enterococcus faecalis* (8.3%), *Streptococcus viridians* (8.3%) and *Listeria monocytogenes* (8.3%) were isolated. CSF culture was more sensitive for diagnosis of APM than blood culture in this study because the incidence of culture positive was more in CSF than blood (eight CSF culture-positive cases and six blood culture-positive cases were detected among 44 children). In the study of Wai Mar Tin, 2005,[9] the most common organism was *Haemophilus influenzae* (36.7%), followed by *Neisseria meningitidis* (20%), *Staphylococcus aureus* (16.7%) and *Streptococcus pneumoniae* (16.7%).[9] There was no *Haemophilus influenzae* detected in this study.

Out of eight CSF culture-positive cases in this study, four (50%) culture-positive cases belonged to two months to one year age group and the organisms infected were *Streptococcus pneumoniae, Enterococcus faecalis, Neisseria meningitidis* and *Listeria monocytogenes* in this age group. Pre-treatment CSF culture or lumbar puncture within 2 hours of antibiotic administration revealed 74.8% of culture-positive cases in a study done in India, 2011.[10] Therefore, the etiology of APM among children in this study had not been well characterized due to prior treatment with antibiotics before evaluation.

Out of six blood cultures-positive cases in this study, three (50%) belonged to less than two months of age and the organisms infected were *Staphylococcus aureus, Streptococcus viridians* and *Escherichia coli.* Half of *Staphylococcus aureus* were resistant to flucloxacillin+amoxicillin and vancomycin in this study. *Staphylococcus aureus* isolates were resistant to cloxacillin (50%) in the study of Wai Mar Tin, 2005.[9]

Two *Neisseria meningitidis* isolates were 100% resistant to cefotaxime, but both were susceptible to ampicillin, ceftazidine, cefoperazon+sulbactam, gentamicin, ciprofloxacin and chloramphenicol in this study. In the study of San Thanda, 2010,[2] *Neisseria meningitidis* isolates were 100% resistant to cefotaxime, ampicillin and gentamicin but all were susceptible to benzyl penicillin, chloramphenicol, ceftriaxone, ceftazidime and amikacin. In the case of *Neisseria meningitidis* isolates, the great majority were susceptible to penicillin and ampicillin, although strains with reduced susceptibility have been reported in Europe, South Africa and the United States.[10]

Two *Escherichia coli* isolates were totally sensitive to ceftazidine and totally resistant to cefotaxime, ceftriaxone, gentamicin, ciprofloxacin and chloramphenicol in this study. In a study done at Federal Medical Centre, Niger, *Escherichia coli* isolates were sensitive to chloramphenicol (71.5%) and gentamicin (85.7%).[10]

One *Streptococcus pneumoniae* isolate was sensitive to oxacillin, piperacillin+tazobactam, ceftazidine, cefoperazon+sulbactam, ciprofloxacin and chloramphenicol and resistant to cefotaxime and ceftriaxone in this study. In the study of Wai Mar Tin, 2005,[9] *Streptococcus pneumoniae* isolated cases were ceftriaxone resistance (28.6%), cefotaxime resistance (28.6%) and penicillin resistance (14.3%).[9] There has been a worldwide increase in rate of penicillin and cephalosporin resistance among infection with *Streptococcus pneumoniae.*[11]

Multidrug resistance was seen in one *Enterococcus faecalis* isolate and vancomycin and cloxacillin were effective against *Enterococcus faecalis* in this study. *Enterococcus faecalis,* a natural inhabitant of the mammalian gastrointestinal tract, is naturally resistant to numerous antibiotics and vancomycin is one of the last line of defense for treating serious *Enterococcus faecalis* infection.[12]

One *Streptococcus viridian* isolate was sensitive to ampicillin, oxacillin, cloxacillin, benzyl penicillin, ciprofloxacin and chloramphenicol. One *Listeria monocytogenes* isolate was sensitive to piperacillin+tazobactam, ceftazidine, cefoperazon+sulbactam, gentamicin, amikacin and ciprofloxacin. In this study, there was an increasing antibiotic resistance among the major pathogens.

Acute complications were found in 25% among males and also 25% among females. There were three expired cases (12.5%) among males and one expired case (5%) among females. Among 44 children, there were 11 cases (25%) with acute complications and four expired cases (9.1%). Among 12 culture-positive cases, five cases had acute complications and one child expired with culture-positive.

Among 32 culture-negative case, six children had acute complications and three children expired with culture negative. Persistent fever and quadriparesis/quadriplegia (13.6% each) were the commonest

acute complications in this study. The acute complications were quadriplegia/quadriparesis (10.9%), persistent fever (9.4%), hemiplegia/hemiparesis (6.2%) and hydrocephalus (6.2%) in the study of Wai Mar Tin, 2005.[9] *E. coli was* isolated from an expired case of one month old boy from periurban area presenting with fever, fit and acute gastroenteritis. *E. coli* growth was resistant to cefotaxime that was given empirically. Although two *Neisseria meningitidis* isolates were totally resistant to cefotaxime, they responded well to cefotaxime *in vivo*. Therefore, the host factor is one of factors against infection. The overall mortality rate was 9.1% in this study. In other studies done on meningitis, the mortality rate was 7.8% at YCH, 2005[10] and 6.45% at MCH, 2010.[2]

Conclusion

APM can be difficult to diagnose as the symptoms and signs are often non-specific, especially in young children. Most of the bacterial isolates from this study were resistant to currently using empirical antibiotics (cefotaxime and ceftriaxone). Surveillance for antibiotics resistant pathogens is particularly important in developing countries, where unregulated use of antibiotics in the general community is common.

Information obtained from this study will be beneficial to establish clinical profile, bacterial etiology and antibiotic sensitivity of isolated bacterial organisms of APM in children to reduce morbidity and mortality.

Recommendation

In this study, it was not possible to obtain all the CSF and blood specimens prior to antibiotics therapy because some patients already had antibiotics before admission, or CSF collection was usually performed after commencing antibiotic in children. Thus, this may have resulted in negative cultures. Periodic review of causal organisms of APM and their antimicrobial sensitivity are an important part of clinical practice and it can generate data to improve rational prescribing of antimicrobial agent and guide prevention strategies.

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