East African Medical Journal Vol. 80 No. 9 September 2003
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NEONATAL BACTERIAL MENINGITIS AT THE NEWBORN UNIT OF KENYATTA NATIONAL HOSPITAL

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ABSTRACT

Background: **Meningitis occurs in up to one third of neonates with septicaemia. Diagnosis is difficult due to its non-specificity of signs and symptoms. While neonatal septicaemia is a common problem at Kenyatta National Hospital (KNH), there are no recent data on the incidence and clinical characteristics of neonatal meningitis at the hospital.**
Objective: **To evaluate the prevalence and the bacterial aetiology of meningitis in neonates at the Newborn Unit (NBU) of KNH.**
Design: **Descriptive cross-sectional study.**
Setting: **Newborn Unit of Kenyatta National Hospital, Nairobi, Kenya.**
Subjects and methods: **Lumbar punctures were performed on eighty-four neonates with suspected sepsis based on specified clinical criteria. Cases were defined as meningitis if the cerebrospinal fluid (CSF) was positive for bacteria by Gram stain, aerobic bacterial culture or latex particle agglutination assay.**
Results: **The prevalence of meningitis amongst cases of suspected sepsis was 17.9%. The male:female ratio was l.5:1 mean birth weight 2116.7 grams (1682.2-2551.2) mean gestational age 35.7 weeks (32.6-38.8) and the mean postnatal age was 4.1 days (2.7-5.4) with none of the parameters being significantly different from those without meningitis. Feed intolerance and lethargy were the most common clinical features, present in 73.3% and 60% of patients with meningitis respectively. Neonates with meningitis had a higher mean CSF protein value (2.67 g/L vs 1.97 g/L, p=0.367) and a significantly higher mean CSF white cell count (21 cells/mL vs 7 cells/mL, p=0.001). The most common aetiological agents were *Escherichia coli* (46.7%). Group B. *Streptococci* (26.7%) and *Klebsiella pneumonia* (13.3%). Most blood and CSF isolates were resistant to ampicillin and gentamicin but showed good *in-vitro* sensitivities to amikacin, ceturoxime and the third generation cephalosporins (ceftriaxone, ceftazidime and cefotaxime). Blood cultures were positive in only 53.3% of neonates with meningitis.**
Conclusion: **Neonatal bacterial meningitis is an important clinical problem at KNH with a prevalence of 17.9% and amongst cases of suspected sepsis. *E. coli* and Group B *Streptococci* were the most common aetiological pathogens. Blood cultures were negative in almost half of the patients with meningitis. Resistance to the commonly employed first-line antibiotics (penicillin and gentamicin) is high and a chance of empirical antibiotic use for neonates with suspected sepsis is recommended.**

INTRODUCTION

Meningitis occurs more commonly during the first month of life than during any other subsequent period and it is associated with high morbidity and mortality (1,2,). The incidence of neonatal meningitis in western countries varies from 0.2-0.5 cases per thousand live births but much higher rates of 1.1-1.9 per 1000 have been reported from developing countries (3-6). There are no recent data on the incidence, clinical characteristics, morbidity and mortality patterns of neonatal meningitis in Kenya. Two studies on neonatal sepsis from Kenyatta National Hospital (KNH) in the early eighties identified meningitis in 4.4% and 5.4% of 89 and 166 neonates with suspected sepsis respectively, but cerebrospinal fluid (CSF) analysis was not done on all recruited patients in both the studies for various reasons (7,8).

The early signs and symptoms of neonatal meningitis are very non-specific and indistinguishable from those of septicaemia and other non-infective causes such as birth asphyxia, respiratory distress syndrome and hypoglycaemia amongst others (2,3,9). A high index of suspicion is therefore necessary and

laboratory support essential to make a diagnosis and offer appropriate treatment. Since blood cultures have been reported negative in up to 50% of cases of neonatal meningitis, examination of CSF is the only confirmatory method of establishing a diagnosis (4,10). Use of antigen detection tests such as the latex particle agglutination (LPA) test has been recommended in developing countries where laboratory facilities may be limited (11). Besides providing an early aetiologic diagnosis, the LPA test is useful in instances where pre-treatment with antimicrobials may affect culture yields. Whereas *Escherichia Coli (E. coli)* and Group B *Streptococci* (GBS) cause the majority of neonatal meningitis in the developed countries, *Klebsiella* species has been the most common CSF bacterial pathogen isolated in studies from Kenya, Jordan and Ethiopia (5-9).

Up to one-third of all neonates with sepsis develop meningitis (3,9). Under-reporting is common but incidence rates of neonatal sepsis vary from 1.0-8.1 cases per thousand live births in western countries to 10-50 per 1000 live births in developing countries (2,3). Prevalence rates of neonatal sepsis have been high at KNH; a suspected sepsis rate of 56% (300 of 532 neonatal admissions) was recorded in a recent audit of newborn unit (Mukhwana RO, MMed Thesis in Paediatrics, University of Nairobi) and confirmed sepsis in 16.7% of 716 neonates (12).

In view of our high neonatal sepsis rate and the fact that a third of these patients may have meningitis, we felt that many cases of this potentially fatal disease were going undetected. This study was therefore set out to look for the proportion of neonates admitted with suspected sepsis who develop meningitis and to specifically identify the CSF bacterial pathogens along with their antibiotic sensitivities. The results of the study could affect the antibiotic policy implications in form of both the initial choice of antimicrobial agents and the duration of therapy of neonates with suspected sepsis, and hopefully reduce the high morbidity and mortality associated with this disease.

MATERIALS AND METHODS

This was a descriptive cross-sectional study carried out between 8th August and 1st December 1999 at the newborn unit of KNH, a secondary level care centre.

Population and case definition: All consecutive patients admitted to the unit with suspected sepsis based on specified clinical criteria were recruited immediately before first-line (benzyl penicillin and gentamicin) or change over to second line antibiotics (a second or third generation cephalosporin and amikacin) were initiated. Neonates whose parents/guardians declined to give consent and those with contra-indications to a lumbar puncture were excluded. The required sample size was 73 using the appropriate statistical formula for a descriptive cross-sectional study. The estimated prevalence was assumed at 5% based on the local estimates of 4.4-5.5% (7,8). The level of statistical significance was set at 0.05 as was the margin of precision error. All patients had a complete medical history taken from the parent/guardian and presence of any maternal/neonatal risk factors documented. A complete physical examination was also performed and specified signs of sepsis looked for as per a standard proforma. A lumbar puncture was done aseptically on each patient and blood taken for specific laboratory tests. Cases were classified as meningitis if their CSF was positive for bacterial pathogens by Gram stain, aerobic bacterial culture or LPA assay. The rest of the cases of suspected sepsis were classified as "no meningitis".

Laboratory methods: Approximately 0.5-1.0 millilitres (ml) of CSF obtained aseptically via a lumbar puncture was collected in two specimen bottles (a plain sterile and a fluoride bottle) and taken immediately to the laboratories in the Department of Chemical Pathology and Microbiology, KNH. CSF cell counts were done using the counting chamber of an Improved Neubauer Chamber filled with well mixed diluted CSF. CSF glucose levels were assayed by the glucose oxidase colorimetric technique (Technicon Instruments, USA), while the CSF protein level was determined by the trichloroacetic acid microprotein method (Sigma Diagnostics, USA). The sediment of centrituged CSF from the sterile bottle was inoculated using a sterile loop onto chocolate, blood and MacConkey agar plates and incubated at 35-37° degrees overnight in candle extinction jars to provide 5-8% carbon dioxide and the plates read every 24 hours for three days. In case of a growth, the isolates would be processed and identified by standard bacteriological techniques.

Antibiograms of isolates were performed by the NCCLS (National Committee on Clinical Laboratory Standards) plotocols of disc diffusion techniques (15,16). Part of the sediment from the centrifuged sample was stained by the standard Gram stain technique. The supernatant from the same specimen was heated for five minutes in a boiling water bath, cooled to room temperature and tested against specific bacterial antigens, namely GBS, *E. coli* (K1), *H. influezae* type b, *S. pneumoniae* and *N. meningitidis* ABCY W135 using the Wellcogen Bacterial Antigen Kit by Murex Biotech Ltd, UK.

Two ml of blood was also withdrawn from a peripheral vein from each patient after adequate skin preparation. One ml of blood was placed into a sterile blood culture broth bottle, 0.5 ml into a sequestrin bottle and 0.5 ml in a fluoride bottle and the specimens taken immediately to the respective laboratories. A total blood count was performed at the Department of Haematology, KNH, using the Coulter Counter T-660 machine with differential cell counts being done manually from a peripheral blood film. The blood glucose level was analysed at the Department of Chemical Pathology, KNH using the glucose oxidase colorimetric method. Blood culture bottles were incubated at 35-37°C and sub-cultured 24 hours later onto standard solid media (5% sheep blood, chocolate and MacConkeys agar plates). These were re-incubated (blood and chocolate agar in candle extinction jars) and inspected at 24 hour interval for growth. In case of a growth, the isolates were processed as per standard techniques. The specimens were declared sterile if there was no growth seen after 72 hours of incubation.

Ethical considerations: Approval was obtained from the Ethical and Scientific Review Committee of the hospital. Informed verbal consent was also taken from the parents/ guardians of the neonates recruited into the study following a full explanation of the study protocol.

Data analysis: Statistical analysis of data was carried out using the SPSS 8.0 program (SPSS Inc. Chicago, USA). Means of quantitative data were compared using the student's t-test and Mann Whitney U-test where applicable while the

Chi-square and Fisher's exact tests were used for qualitative data. Correlations were tested using, the Pearson and Spearman coefficients and the phi statistic. A p-value of less than 0.05 was considered significant.

RESULTS

Of the 106 patients that satistfied the inclusion criteria, 22 were excluded for various reasons (11 had failed lumbar puncture, seven had grossly bloody CSF that could not be analysed by LPA assay, three had contraindications to lumbar puncture and the guardian of one patient refused to give consent). Fifteen of the 84 patients studied had meningitis as per the case definition, giving an overall prevalence rate of 17.9%.

Table 1, details the patients' demographic data. There were no statistically significant differences in the male to female ratios, mean birth weights, mean gestational ages and mean post-natal ages between those with and without meningitis. There was also no difference in the proportion of patients with antibiotic use and the duration of such use amongst the two groups of patients. The predisposing factors were also not significantly different in patients with suspected sepsis, with or without meningitis (Table 2).

Table 1

Summary of some demographic data of study patients

Variable	all (n=84)	Meningitis (n=15)	No. Meningitis (n=69)	P-value
Male:female ratio	1.15:1	1.5:1	1.1:1	0.582#
Mean birth weight (gms)	2236.7 (1606.9-2574.3)	2116.7 (1682.2-2551.2)	2262.8 (2047.1-2474.8)	0.550*
Mean gestational age (wks)	35.1 (34.3-35.9)	35.7 (32.6-38.8)	35.0 (31.1-38.9)	0.675*
Mean post-natal age (days)	4.9 (3.8-5.9)	4.1 (2.7-5.4)	5.0 (3.8-6.3)	0.910*
Prior antibiotic use	60(71.4%)	11(73.3%)	49(71%)	1.000##
Mean antibiotic use (days)	1.80 (1.45-2.07)	1.47 (0.84-2.09)	1.87 (1.52-2.22)	0.282**

*= Student's test **= Mann Whitney U test, #= Chi-square test, ##= Fisher's exact test

Table 2

Prevalence of risk factors amongst study patients (n=84)

Risk factor	All (n=84) No. (%)	Meningitis No. (%)	No meningitis No. (%)	P-value
PROM **	16 (19)	5 (33.3)	11 (15.9)	0.120*
Maternal fever	3 (3.6)	0 (0)	3 (4.3)	1.000#
Chorioamnionitis	8 (9.5)	2 (13.3)	6 (8.7)	0.629#
Prematurity	51 (60.7)	10 (66.7)	40 (60.0)	0.602*
Low birth weight	50 (59.5)	10 (66.7)	40 (60.0)	0.534*
Resuscitation at birth	16 (19.0)	2 (13.3)	14 (20.3)	0.725#

** PROM= Prolonged Rupture of Membranes, *= Chi-square, # =Fisher's exact test

Table 3

Some clinical features of study patients

Clinical Feature	All (n=84) No. (%)	Meningitis No. (%)	No Meningitis No. (%)	P-value
Feed intolerance	66 (78.6)	11 (73.3)	55 (79.7)	0.729#
Lethargy	49 (58.3)	9 (60.0)	40 (58.0)	0.885*
Seizures	13 (15.5)	4 (26.7)	9 (13.0)	0.235#
Skin changes	49 (58.3)	9 (6.0)	40 (58.0)	0.885*
Bulging fontanelle	12 (14.3)	4 (26.7)	8 (11.6)	0.214#
Neck retraction	4 (4.8)	2 (13.3)	2 (2.9)	0.145#
Respiratory signs	35 (41.7)	6 (40.0)	29 (42.0)	0.885*

*= Chi-square test, #= Fisher's exact test

Table 4

CSF biochemistry parameters and cell counts of study patients

Variable	All Mean (95%CI)	Meningitis Mean (95%CI)	No Meningitis Mean (95%CI)	P-value*
CSF Protein (g/L)	2.10(1.71-2.49)	2.67(1.07-4.28)	1.97(1.62-2.32)	0.376
CSF Glucose(mmol/L)	3.60(2.90-4.20)	3.19(1.40-4.97)	3.65(2.91-4.39)	0.616
CSF Glucose as % of RBS	74.0(64.0-85.0)	63.0(37.0-88.0)	77.0(65.0-89.0)	0.299
CSF WBC count (cells/mL)	9.0(7.0-12.0)	21.0(13.0-29.0)	7.0(5.0-9.0)	0.001
CSF RBC count (cells/mL)	11.0(7.0-15.0)	14.0(2.0-26.0)	1.0(6.0-15.0)	0.551

* Student's t-test

Table 5

CSF bacterial isolates and their antibiotic sensitivity patterns (n=4)

Antibiotic	*Klebsiella spp.*(n=2)	Group B. *Streptococci*	*Enterobacter spp.*
Ampicillin	R	S	R
Gentamicin	R	R	R
Amikacin	S/R	S	S
Chloramphenicol	R	R	R
Cefuroxime	S	S	S
Ceftazidime	R	S	S
Ceftriaxone	S	S	S
Cefotaxime	S	S	S

S = Sensitive, R = Resistant

Feed intolerance, lethargy and skin changes (poor colour, mottling and scleraema) were the most common features in the study patients, and were almost equally common in the two groups of patients with and without meningitis (Table 3). The meningeal signs, viz. bulging fontanelle and neck stiffness, were present in a higher proportion of patients with meningitis compared to those without meningitis, but not significantly so. Almost equal proportions of patients in the two groups also had features of respiratory distress.

Table 4 shows the CSF biochemistry parameters and cell counts of study patients. Mean CSF protein was higher in the patients with meningitis than those without meningitis but did not reach significant levels. Mean CSF white cell count was significantly higher in study patients with meningitis (21 cells/mL vs 7 cells/mL, p=0.001, Students t-test) (Figure 1).

Figure 1

Mean CSF white cell count of study patients with and without meningitis

Figure 2

CSF detection yield of bacterial pathogens by various methods

Figure 3

Blood culture isolates from patients

Figure 4

Antibiotic sensitivities of blood culture isolates from study patients

Fifteen cases of bacterial meningitis were positively identified by various methods: one by Gram stain, four by CSF culture and thirteen by the LPA method (two cases were identified by more than one method of detection) (Figure 2). LPA had the highest yield and Gram stain the lowest. The most common aetiological agent was *Escherichia Coli* (n=7), followed by Group *B Streptococci* (n=4) and *Klebsiella pneumoniae* (n=2). There was one case each of *Enterobacter cloacae, Haemophilus influenzae* and *Strepococcus pneumoniae.*

CSF cultures were positive in only four (4.8%) cases; there were two growths of *Klebsiella pneumoniae,* one of group B *Streptococci* (GBS) and one of *Enterobacter cloacae.* The antibiotic sensitivity pattern is as shown in Table 5. All four isolates were resistant to both gentamicin and chloramphenicol, and only GBS was sensitive to ampicillin. Three (75%) of the organisms were sensitive to amikacin and there was 100% *in-vitro* sensitivity to cefuroxime, ceftriaxone and cefotaxime.

Blood cultures were positive in 38 (45.2%) of the 84 study patients, with *Klebiella spp.* being the most common pathogen identified. The prevalence of the various blood culture isolates and their antibiotic sensitivities are shown in Figures 2 and 3 respectively.

Blood cultures were positive in 8 out of 15 or 53.3% of patients with meningitis. There was no significant association between blood culture positivity and case of meningitis (p=0.487, Chi-square test) and they did not correlate well (phi statistic 0.076, p=0.487). Blood cultures and CSF cultures did also not show a significant association (p=0.324, Fisher's exact test) and did not correlate well either (phi statistic 0.134, p=0.220).

Although mortality as an outcome of meningitis was not one of the study objectives, it was found to be significantly higher amongst study patients with meningitis (10/15 or 66.7%) than those without meningitis (22/69, 31.9%) (p=0.012, Chi square test).

DISCUSSION

Neonatal bacterial meningitis is an important clinical problem at this hospital with a prevalence rate of 17.9% of 84 patients with suspected sepsis. This is much higher than the previously locally reported prevalence rates of 4.4% (7) and 5.4% (8). However, lumbar punctures were not performed on all neonates with suspected sepsis in both previous studies, which also relied exclusively on CSF culture growths for case identification of meningitis. Our study, on the other hand, also utilised a bacterial antigen detection kit, which substantially increased the CSF yield. The high prevalence rate is probably in keeping with the 10 to 100 fold higher incidence rates of neonatal meningitis reported from developing countries as compared to that seen in the more developed regions (1,2,4,10,15).

The male: female ratio amongst our study patients with meningitis was 1.5:1, comparing well with the slight male preponderance noticed by other studies (4,10). Low birth weight and prematurity, known risk factors for neonatal sepsis and meningitis, were equally prevalent amongst neonates with and without meningitis in our study. This may be explained by the fact that the "no meningitis" group was itself comprised of neonates with clinically suspected sepsis, which would have higher numbers of preterm and low birth weight babies than would be expected in a general newborn population. A few recent studies have also reported equal or slightly higher rates of meningitis amongst term than preterm babies (4,10,16). Maternal risk factors were also not very prevalent in study subjects with meningitis. It was unfortunately not possible to perform maternal septic screens including vaginal swabs to objectively assess some of these risk factors. Known maternal risk factors for neonatal meningitis have been observed in less than 30% of instances by previous author (4,6,15).

Clinical features of neonates with meningitis were mainly non-specific, the most common being feed intolerance and lethargy, and the features were similar to those with suspected sepsis but without meningitis. Lumbar puncture for CSF analysis, though often left out, therefore remains an integral part of the septic screen for neonate with suspected sepsis in our set-up.

CSF cell counts (which were significantly higher in study patients with meningitis) and CSF biochemical parameters are useful guides as to the presence of disease, especially if CSF cultures are non-yielding. Gram stain was positive in only one CSF specimen of the fifteen cases of meningitis in our study, quite in contrast to the 70-80% Gram stain yield reported elsewhere (17). The poor yield of the Gram stain method at this institution has been noted down the years, from anecdotal reports by colleagues as well as from personal experience. Technical factors may be responsible for the poor yield, although precautions were taken during this study to process the CSF specimen immediately and stain the centrifuged sediment using standard technique (13). An in-house study within the department of microbiology is probably necessary to look into this issue.

Our overall CSF culture yield of 4.8% (4 out of 84 patients with suspected sepsis) was similar to the previous locally reported rates of 4.4% - 5.4% (7,8) and may have been influenced by the high rate of antibiotic use amongst study subjects. Anaerobic cultures and post-mortem examinations, not done due to financial and logistical constraints, could have improved the overall yield.

Antigen detection kits such as the LPA assay used in this study, which substantially increased our CSF yield, have been widely used as adjuncts for diagnosis of sepsis and meningitis with sensitivities and specificities of 81-100% recorded by researchers in both the developing and developed countries (11,18). Their use is especially recommended in instances where antibiotic use has been commenced before microbiological analysis of patients' body fluids has been possible (1, 2). The major drawback of such kits is that they do not give antibiotic sensitivity patterns of any pathogen identified. However, positive identification of a bacterial pathogen in the CSF of a patient has important implications in dosage and duration of empirical antimicrobial therapy. The actual choice of drugs used may be based on the results of regular bacterial surveillance of the unit concerned.

Escherichia coli and Group *B Streptococci* were interestingly the most prevalent CSF bacterial isolates, causing 11 of the 15 cases of meningitis. These two organisms are the most common causes of neonatal meningitis in the developed world, but have been infrequently reported in studies from third world countries (1,2,4,5,8,l0,15). *E. coli* was, however, the second most common bacterial isolate in a recent Ethiopian study (6) and GBS meningitis has been documented in a local study on perinatal GBS disease (19), *Klebsiella*, an important cause of neonatal meningitis in developing countries (5,6,8), accounted for two of the four CSF culture and 19 of 38 (51%) blood culture growths. Antigen detection kits that test for Gram negative bacteria such as *Klebsiella spp*, would be useful in areas with a high prevalance of such organism, but are currently not available.

Because of the small numbers of bacterial isolates on CSF culture, it was difficult to make firm conclusions on the antibiotic sensitivities against the aetiological agents causing meningitis. On the other hand, blood cultures were positive in 45.2% of the study population and the sensitivity patterns showed a distinctive trend. Gram positive organisms were uniformly resistant to gentamicin and with the exception of GBS, to ampicillin as well, but most were sensitive to chloramphenicol, cefuroxime and the third generation cephalosporins. The majority of Gram negative isolates were highly resistant to the first-line antibiotics, ampicillin and gentamicin, but again showed good *in-vitro* sensitivity to the new cephalosporins and amikacin. *Pseudomonas* isolates were sensitive to some cephalosporins and to the piperacillin/tazobactam combination.

Gentamicin has been used as one of the first-line empirical antibiotics for the treatment of suspected neonatal sepsis at KNH for the last two decades, but recent local studies (l2,20) have documented high resistance to gentamicin, similar to what has been seen in our study. The good sensitivities obtained against cephalosporins and the fact that they have better CSF penetration than aminoglycosides, makes them appropriate agents for empirical therapy whilst awaiting definite culture and sensitivity reports. Gentamicin needs to be withdrawn and replaced with an affordable and available third generation cephalosporin and/or amikacin. Plasmid mediated resistance to cephalosporins is a growing concern where these drugs have been in use for some time, and "cycling" of antibiotics for certain periods of duration is being advocated to avoid emergence of multidrug resistant organisms (12,21).

Blood cultures were negative in 46.7% of neonates with meningitis, comparable to the 52% negative blood culture rate by Shattuck and Chonmaitree (10), and there was no correlation between blood culture positivity and cases of meningitis. The results further re-emphasise the importance of not relying solely on blood cultures nor neglecting to perform lumbar punctures on neonates with suspected sepsis, as otherwise nearly half the babies with meningitis would remain undetected.

ACKNOWLEDGEMENTS

To the members of staff, Departments of Paediatrics and Child Health, Microbiology, Haematology, Biochemistry and Newborn Unit, KNH/UON, for their kind assistance and guidance. To Dr Juzar Hooker for his guidance and Zahir Mamdani for his expert help in computer related matters.

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