Brief Report

Acute Bacterial Meningitis at the ‘Complexe Pédiatrique’ of Bangui, Central African Republic

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Summary

To precize the aetiologies of children meningitis and the susceptibility to antibiotics of bacteria responsible for meningitis in Bangui, we conducted a prospective study between October 2004 and September 2005, at the ‘Complexe Pédiatrique de Bangui’, Central African Republic (CAR). Children from 1 day to 16 years with suspected meningitis and who underwent a lumbar puncture were enrolled. Gram staining, culture on chocolate blood medium, cell count, biochemistry (protein level, glucose ratio), capsular antigen detection were performed for each cerebrospinal fluid. MICs were determined by the E-test method. Four hundred and seventeen patients were enrolled during the study period; 130 were proven acute bacterial meningitis and 37 probable bacterial meningitis. Among proven bacterial meningitis, Streptococcus pneumoniae was the most common organism responsible for meningitis (62 cases, 48%) followed by Haemophilus influenzae (46 cases, 35%) and by Neisseria meningitidis and Salmonella sp. (8 cases, 6% each). Ninety-four percent and 96% of S. pneumoniae strains tested remain susceptible to benzylpenicilline and chloramphenicol, respectively. A beta-lactamase was detected in 92% of H. influenzae strains tested. However, MICs 50% and 90% for amoxicillin were found to be 1 and 4 mg/l, respectively and 33% of these strains were resistant to chloramphenicol. The global mortality rate was 35% (59/167). This mortality rate was 47% for S. pneumoniae, 33% for H. influenzae, 62% for Salmonella sp. and 13% for N. meningitidis. The probabilistic treatment with ampicillin and chloramphenicol usually administered for children meningitis in Bangui must be reconsidered particularly in cases of H. influenzae meningitis. It is of importance to reduce the presentation delays of children with suspected meningitis in Bangui. The H. influenzae b immunization would allow a dramatic reduction of meningitis cases and deaths in Central African children.

Key words: Bacterial meningitis, Central Africa, Streptococcus pneumoniae, Haemophilus influenzae.

Introduction

Acute bacterial meningitis (ABM) remains a major cause of morbidity and mortality particularly in sub-Saharan African children [1]. Classically, Streptococcus pneumoniae, Haemophilus influenzae and Neisseria meningitidis are responsible for the majority of ABM in African children. H. influenzae meningitis is preventable with the use of conjugate vaccines and the incidence of the disease has dramatically declined in areas where this immunization is in place. However, in Central African Republic (CAR), H. influenzae immunization is not yet included in the Expanded Program of Vaccination and the importance of the disease in children has to be evaluated. Monitoring the changing susceptibilities of bacteria to antibiotics in use in cases of meningitis is necessary for the actualization of the probabilistic antibiotic regimens. Thus, we have undertaken a prospective study at the Complexe Pédiatrique de Bangui (CPB), to identify the causative agents of ABM in children in Bangui and to

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evaluate their susceptibility to the antibiotics that are in used in first line as probabilistic treatment. The CPB, with a capacity of 240 beds, is the referral pediatric hospital of Bangui, a city of about 650,000 inhabitants, with annually admission rate of 12,000 patients from birth to 16 years.

Methods

From 1 October 2004 to 30 September 2005 demographic and clinical data were collected prospectively for all children who presented at the CPB with a suspicion of meningitis and for whom a lumbar puncture was performed. A diagnosis of ABM was confirmed when a Gram stain on cerebrospinal fluid (CSF) revealed bacterial bodies; or when culture of CSF yielded a pure bacterial growth after 24 h or 36 h of incubation on chocolate-agar plate and agglutination test (Slidex pneumo-kit, bioMérieux, Marcy l’Étoile, France). A diagnosis of probable bacterial meningitis (PBM) was made if the Gram stain, the culture and the detection of capsular antigens were negative but white blood cell (WBC) count in CSF was greater than normal (>20 WBC/mm³) in neonates and >10 WBC/mm³ in others) with predominance of polymorphonuclears, associated with an increase in CSF protein level (>0.45 g/L) and decrease in the ratio of glucose in CSF to blood (<0.6).

Antibiotic treatment was initiated immediately on admission. In CAR, the current recommendations for first line treatment of children meningitis are: ampicillin 100 mg/kg/day and chloramphenicol 100 mg/kg/day for 10 days. This treatment was reassessed when bacteriological results are available.

Bacteria were identified using standard methods (API NH strips, bioMérieux) for N. meningitidis and H. influenzae; susceptibility to optochin on blood agar plate and agglutination test (Slidex pneumo-kit, bioMérieux) for S. pneumoniae. A serological typing was systematically performed for N. meningitidis (Pastorex meningitis, Bio-Rad, Marnes la Coquette, France) and H. influenzae b (Statens Serum Institute, Denmark).

Susceptibility to antibiotics was determined by diffusion method, according to the recommendations of the Antibiogram Comity of the French Society of Microbiology (CA-SFM). MICs for S. pneumoniae strains were determined by the E-test method (AB Biodisk, Dalvén, Sweden) for penicilline G, ampicillin, cefotaxime, chloramphenicol and tetracycline on a 5% sheep-blood agar plate. For H. influenzae strains, a chromogenic method (Cefinase, bioMérieux) was systematically used to detect the presence of a beta-lactamase and MICs for ampicillin, cefotaxim and chloramphenicol were performed by the E-test method on HTM medium. Susceptibility testing was analyzed according to the recommendations of the CA-SFM (edition 2006). S. pneumoniae ATCC 49619 and H. influenzae ATCC 49766 were used as control strains.

Statistical Analysis

Data were analyzed using the Epi Info version 3.3.2 (CDC, Atlanta, GA, USA) and STATA intercooled 8.0 (Stat corp., College Station, Texas, USA) software programs. Results were presented as proportions and compared using chi-2 or Fisher exact tests. Comparison between ages was carried out using t-Student test. Interpretation of all those tests was done at 0.05 α level.

Results

From 1 October 2004 to 30 September 2005, 417 patients between 1 day and 16 years, underwent a lumbar puncture at the CPB for suspicion of ABM (3.5% of admissions). Their mean age was 44 months (median 17 months) and the sex ratio M/F was 1.2. One hundred and thirty (130) children met the criteria for proven ABM and 37 for PBM (Table 1). The mean age was different between these 167 children and the ones for whom a diagnosis of ABM was not retained: 58 and 35 months, respectively, (p = 0.003).

<table>
<thead>
<tr>
<th>Age group</th>
<th>S. pneumoniae</th>
<th>H. influenzae</th>
<th>N. meningitidis</th>
<th>Salmonella spp.</th>
<th>Streptococcus agalactiae</th>
<th>Other organisms</th>
<th>No organism isolated</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 month</td>
<td>3 (1; 33%)</td>
<td>2 (2; 100%)</td>
<td>–</td>
<td>2 (1; 50%)</td>
<td>–</td>
<td>–</td>
<td>1 (1; 100%)</td>
<td>16 (7; 44%)</td>
</tr>
<tr>
<td>1–3 months</td>
<td>4 (1; 25%)</td>
<td>2 (-)</td>
<td>–</td>
<td>1 (-)</td>
<td>–</td>
<td>1 (-)</td>
<td>1 (1; 100%)</td>
<td>8 (1; 13%)</td>
</tr>
<tr>
<td>4–11 months</td>
<td>11 (4; 36%)</td>
<td>24 (6; 25%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>9 (1; 11%)</td>
<td>48 (13; 27%)</td>
<td>57 (15; 31%)</td>
</tr>
<tr>
<td>1–4 years</td>
<td>15 (2; 22%)</td>
<td>12 (4; 33%)</td>
<td>2 (-)</td>
<td>2 (2; 100%)</td>
<td>–</td>
<td>–</td>
<td>3 (2; 38%)</td>
<td>35 (11; 31%)</td>
</tr>
<tr>
<td>&gt;4 years</td>
<td>35 (21; 60%)</td>
<td>6 (3; 50%)</td>
<td>6 (1; 17%)</td>
<td>–</td>
<td>–</td>
<td>13 (2; 15%)</td>
<td>60 (27; 45%)</td>
<td>52 (22; 45%)</td>
</tr>
<tr>
<td>All</td>
<td>62 (29; 47%)</td>
<td>46 (15; 33%)</td>
<td>8 (1; 13%)</td>
<td>8 (5; 63%)</td>
<td>3 (-)</td>
<td>3 (1; 33%)</td>
<td>37 (8; 22%)</td>
<td>167 (59; 35%)</td>
</tr>
</tbody>
</table>

*aother organisms were 1 Chryseobacterium meningosepticum, 1 Streptococcus pyogenes and 1 Staphylococcus aureus.
Among the 130 cases of proven ABM, \textit{S. pneumoniae} was the most common agent of meningitis in this study (48%), followed by \textit{H. influenzae} (35%), \textit{N. meningitidis} and \textit{Salmonella sp.} (6% each). Serotyping of \textit{S. pneumoniae} was undertaken and serotype 1 was predominant, representing 41% of 44 typed strains (unpublished results). This bacterium was confirmed as aetiologic agent in all age group and was the main etiological agent in children under 4 years (58%). On the contrary, between 4 months and 4 years, \textit{H. influenzae} was the most common isolated organism (43%). \textit{N. meningitidis} was far less common and solely in children over 1 year. \textit{Salmonella enterica} was the only \textit{Enterobacteriaceae} found during this study and five were \textit{Salmonella} typhimurium and three \textit{Salmonella} enteritidis.

The initial Gram staining permitted an accurate aetiologic orientation in 72% of the 130 cases of confirmed ABM (35/46 \textit{H. influenzae}, 46/61 \textit{S. pneumoniae}, 6/8 \textit{N. meningitidis} and 6/8 \textit{Enterobacteriaceae}). Culture was positive for 119 of these cases.

The global mortality rate in cases of confirmed ABM was 39% (59/130), (Table 1). This mortality rate was 47% for \textit{S. pneumoniae} meningitis and 33% for \textit{H. influenzae} meningitis. Five of the eight cases of \textit{Salmonella} meningitis died within 48 h, but only 1 of the 8 \textit{N. meningitidis} meningitis. In the age group >4 years, the mortality rate of \textit{S. pneumoniae} meningitis was 60% (21/35). The mortality rate was at the limit of significance between ABM (39%) and MBP (22%), \((p = 0.054).\)

For the 49 \textit{S. pneumoniae} tested, MIC of benzylpenicillin was 0.032 mg/l for 90% of the strains and 94% of the strains were categorized as susceptible whereas 100% of the strains were susceptible to amoxicillin and cefotaxime. The MICs 90% of chloramphenicol was 2 mg/l and 96% of the strains were categorized as susceptible. On the contrary, solely 38% of the strains were susceptible to tetracycline.

A beta-lactamase was detected in 35 of 38 \textit{H. influenzae} strains (92%). Susceptibility to antibiotics was available for 29 strains for which MICs 50% and 90% of amoxicillin were 1 and 4 mg/l, respectively. All strains remained susceptible to cefotaxime (MIC 90 = 0.032 mg/l), whereas only 67% of them remained susceptible to chloramphenicol (MIC 50 and MIC 90 = 2 and 4 mg/l, respectively).

The eight strains of \textit{N. meningitidis} belonged to three serotypes: 2W 135, 2C and 4A. All these strains remained susceptible to benzylpenicillin (MIC \(\leq 0.02\) mg/l), amoxicillin, cefotaxime and chloramphenicol (MIC \(\leq 0.1\) mg/l). All \textit{Salmonella} strains were resistant to amoxicillin, chloramphenicol and cotrimoxazole but remained susceptible to ceftriaxone and ciprofloxacin.

### Discussion

This prospective study conducted at the referral pediatric facility of Bangui underlines the frequency and severity of bacterial meningitis in central-African children. In this study, \textit{S. pneumoniae} was the most frequent organism responsible for meningitis, followed by \textit{H. influenzae} as already reported in several sub-Saharan Africa countries [2–7]. \textit{N. meningitidis} isolation is uncommon as long as an outbreak does not occur [1]. Isolation of \textit{Salmonella sp.} from CSF represents the only \textit{Enterobacteriaceae} isolated which is surprising although the two serovars are known to have invasive properties. However, the possibility of an immunodepression was not investigated in the infected children. The high frequency of \textit{Salmonella} in cases of meningitis has been previously reported in sub-Saharan Africa studies [3,4,8,9]. This particularity is not clearly explained but the severity of the prognostic is underlined as it was the case in our study.

The high mortality rates with meningitis due to \textit{S. pneumoniae} and \textit{H. influenzae} are similar to those observed in Malawi [4], Ethiopia [3] and Burkina Faso [10] and higher than those notified in Gambia [2]. However, this overall fatality rate was lower than the 51% of death observed in a recent Tanzanian study conducted in a rural hospital [11]. This may be due to the difficulty for reaching a medical facility in the countryside which increases the risk of developing a severe infection.

The presence of a betalactamase in almost all strains of \textit{H. influenzae} (92%) explains the lack of activity of amoxicillin despite an apparent relatively low level of MICs. This weak activity of amoxicillin is worsened by the 34% resistance rate to chloramphenicol. Therefore, the systematic use of the association ampicillin-chloramphenicol as probabilistic treatment of meningitis may explain some fatal outcomes of meningitis due to \textit{H. influenzae} in Bangui.

Although \textit{S. pneumoniae} remains susceptible to commonly used antibiotics, very high rates of mortality in \textit{S. pneumoniae} meningitis have been observed. This disease is known to be a complex and very rapid disorder with central nervous system infection and complications of systemic infection ending with shock and intravascular coagulation [12]. This poor outcome in Bangui is related to delays in attending the consultation, leading to long histories of fever and late access to accurate diagnosis and treatment.

The immediate Gram staining of fresh CSF was helpful for diagnosis orientation. Therefore, and because of the decreased susceptibility of \textit{H. influenzae} to amoxicillin and chloramphenicol, it would be interesting to adapt the initial treatment according to microscopy results. If \textit{S. pneumoniae}, easily identified on smear, is present, amoxicillin remains indicated. In the other cases, ceftriaxone is recommended.
The evidence of a dramatic reduction in invasive H. influenzae infection after routine vaccination of children [13] underlines the urgent need for the inclusion of a combined anti-haemophilus b vaccine in the expanded program of vaccination to achieve a decline of cases in the country. The same attitude would be valuable to reduce the incidence of pneumococcal meningitis. However, the determination of the main circulating serotypes is necessary to devise a vaccine adapted to the African countries before initiating clinical trials.

References