The Changing Profile of Pediatric Meningitis at a Referral Centre in Cape Town, South Africa

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Summary

Background: Pediatric meningitis remains a common cause of childhood morbidity and mortality in developing countries. Knowledge of the causative organisms in a region is of importance in guiding empiric antibiotic regimes and immunization schedules assisting decisions on primary health-care interventions.

Methods: This retrospective review of 557 meningitis cases represents a third pediatric survey conducted over a 3-year period (January 2007 to December 2009) at the same institution and after an interval of 14 years. Cases were identified using cerebrospinal fluid results. Demographic and laboratory variables were collected and meningitis was classified as aseptic/viral, bacterial, septic, tuberculous meningitis (TBM) or fungal.

Results: The commonest form of bacterial meningitis was TBM diagnosed in 22% (n = 126) of children. *Streptococcus pneumoniae* 4% (n = 23) and *Klebsiella pneumoniae* 3% (n = 17) were the next commonest causes of bacterial meningitis diagnosed. *Haemophilus influenzae* meningitis occurred in <1% (n = 3) of cases with a median age of 3 months. Aseptic meningitis remains the commonest category. Human immunodeficiency virus (HIV) testing was requested in 43% (n = 241) of cases; 8% (n = 46) were positive.

Conclusion: TBM remains the commonest cause of pediatric bacterial meningitis in the Western Cape. It is concerning that the percentage of TBM cases out of the total study population has more than doubled compared with that in previous surveys. The low prevalence and young age of *H. influenzae* meningitis cases confirm the benefits derived from *H. influenzae* type b (Hib) vaccination.

Introduction

Due to the focus on the burden of human immunodeficiency virus (HIV), tuberculosis (TB) and malaria in Africa, pediatric meningitis is sometimes forgotten as a significant and often preventable cause of morbidity and mortality [1, 2]. Two pediatric meningitis surveys were previously conducted in our institution, which serves half the population of the Western Cape [3, 4]. A prospective 3-year study from June 1981 till June 1984 concluded the commonest cause of confirmed bacterial meningitis was *Neisseria meningitidis* (11.5%). Tuberculous meningitis (TBM) was responsible for 5% of the cases [3]. A 9-year prospective survey from January 1985 to December 1993 concluded that TBM had become the most predominant cause of bacterial meningitis in the Western Cape. This rise in the incidence of TBM occurred despite low HIV prevalence at the time (~0.3% seroprevalence) [5].

*Neisseria meningitidis, H. influenzae and S. pneumoniae* in sequence were the next commonest causes identified [4].

This study represents the third pediatric meningitis survey at the same institution after a period of 14 years. Factors that may have influenced the etiological profile during this period include: (i) increase in HIV prevalence, (ii) increase in TB prevalence and (iii) introduction of *H. influenzae* type b (Hib) vaccine in July 1999 and pneumococcal conjugate vaccine (PCV) in 2009 to the child Extended Programme of Immunization (EPI) schedule [6].

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Methods

All children under the age of 13 years admitted to Tygerberg Children’s Hospital from 1 January 2007 to 31 December 2009 who had cerebrospinal fluid (CSF) examination indicating meningitis were included in the study. Meningitis was defined as the presence in the CSF of >5 x 10^6/l leukocytes in children older than 2 months and more than 15 x 10^6/l leukocytes in children younger than 2 months; or the presence of a positive CSF culture (viral, bacterial or mycobacterial) or bacteria visible on Gram staining of the CSF [3, 4, 7].

Children who had CSF studies sent to National Health Laboratory Service at the hospital were identified by a data mining process. The CSF results were reviewed, together with other available laboratory data, including C-reactive protein, white cell count and blood culture, by the principal investigator and two experts: an experienced general pediatrician and pediatric neurologist. The types of meningitis were then classified into one of five categories: (i) aseptic/viral meningitis when predominantly lymphocytes were present, with CSF chemistry within normal reference ranges, or when a virus was isolated from the CSF; (ii) bacterial meningitis when bacteria were cultured, seen on Gram stain or bacterial antigen latex agglutination tests were positive; (iii) septic meningitis with unknown cause when the CSF had characteristic features of a bacterial meningitis (high protein, low glucose, polymorph predominance), but blood and CSF cultures were negative; (iv) TBM when *Mycobacterium tuberculosis* was isolated from the CSF and/or gastric aspirate. Or CSF findings suggestive of TBM (high protein, low glucose, lymphocyte predominance) and two of the following criteria: (a) recent poor weight gain (crossing of centile lines on the road-to-health-card); (b) household contact with sputum smear positive tuberculosis; (c) computed tomography scan compatible with TBM; (d) Chest radiograph compatible with primary tuberculosis; (e) positive tuberculin skin test; (f) other clinical specimens positive for acid-fast bacilli; (g) fungal meningitis when fungi were cultured from CSF or a positive India Ink Test on serum or CSF [3, 4].

Bloodstained CSF’s were excluded unless there was an organism cultured on the CSF or the blood culture. The CSF results of children admitted to the pediatric neurology ward were cross-checked with a database of discharge summaries from this ward and cases with uncertain results had their folders reviewed.

CSF was processed according to standard laboratory methods. CSF was not routinely processed for viral culture or polymerase chain reaction (PCR). The use of bacterial latex agglutination tests was discontinued by the National Health Laboratory Service in 2007. In response to the HIV pandemic, the Cryptococcus antigen latex agglutination test was introduced after the previous studies and is performed on request, and the Indian ink stain is routinely performed on all CSF specimens. The HIV status of the studied children was obtained from the laboratory information system and classified as (i) positive, if the HIV PCR was positive in children under 18 months of age or if two HIV enzyme-linked immunosorbent assay tests were positive in a child >18 months, (ii) negative if the child tested enzyme-linked immunosorbent assay or PCR negative (iii) unknown if no laboratory record of being tested.

The study was approved by the Committee for Human Research at Stellenbosch University.

Results

There were 4192 CSF examinations performed in children under 13 years at Tygerberg hospital from 1 January 2007 to 31 December 2009. Five hundred fifty-seven episodes of meningitis were identified in 551 children. There was an annual incidence of 177 episodes in 2007, 144 episodes in 2008 and 236 episodes in 2009. The mean age was 38 months (range of 1 day–163 months); SD 44 months, median 17 months. Figure 1 shows the age distribution of the four most important causes of meningitis. Children with aseptic/viral meningitis or TBM were significantly older compared with those with bacterial meningitis (*p* < 0.01).

Figure 2 shows the different categories of meningitis in absolute numbers. Aseptic meningitis was the commonest identified form of meningitis.

The commonest identified bacteria and the mean age of the children during the episode of meningitis are shown in Table 1.

TBM was diagnosed in 126 episodes, representing 22% of the total sample and 53% of the combined bacterial group. In 10% (*n* = 13) of cases TBM was confirmed by a positive culture for *Mycobacterium tuberculosis* on the CSF. Sixty-two (11%) neonates were included in the study; 81% (*n* = 50) had septic meningitis; and in 72% (*n* = 36), the cause was confirmed by culture. The commonest isolated bacteria were *Klebsiella pneumoniae* (*n* = 11), followed by beta-hemolytic streptococcus group B (*n* = 7), *Escherichia coli* (*n* = 4) and *Serratia marcescens* (*n* = 3). HIV testing was performed in 18% of cases (*n* = 11); none tested positive.

HIV test results were available in 43% (*n* = 241) of cases of which 8% (*n* = 46) proved positive.

Children with TBM were most likely to be tested for HIV (74%), 12% (*n* = 15) tested positive, whereas children with aseptic meningitis were tested least often (26%). Sixty-one percent (*n* = 14) of children with a bacterial meningitis caused by *S. pneumoniae* were tested for HIV, three had a positive result. All
Three children with *H. influenzae* meningitis were tested for HIV, one was positive.

The etiology of meningitis for HIV-infected children was as follows: 39% (*n* = 18) aseptic, 24% (*n* = 11) bacterial, 33% (*n* = 15) TBM and 2% (*n* = 1) fungal. Seven percent (*n* = 37) of meningitis cases had ventriculoperitoneal (VP) shunts. The commonest bacteria associated with VP shunt infection were coagulase negative staphylococcus in 22% (*n* = 8), *Staphylococcus aureus* in 14% (*n* = 5) and *Acinetobacter baumanii* 11% (*n* = 4).

Table 2 compares our study findings with the previous two studies at the same hospital. TBM remains the commonest cause of bacterial meningitis in the Western Cape, with a more than doubled percentage of TBM cases out of the total study population. The number of *N. meningitidis* cases appears to have declined markedly.

**Discussion**

It is of great concern that the number of TBM cases has almost doubled since previous studies [3, 4]. This could be partly attributed to the increased incidence of TB in the Western Cape from 689 cases/100 000 population in 1997 to 909 cases/100 000 population in 2009 [8]. This implies a larger exposure risk to TB in young children who are most susceptible to developing TBM. The increased prevalence of HIV since the 1990s could also have contributed. A previous study at Tygerberg Children’s Hospital reported an HIV prevalence of 13% in children with TBM [9]. The apparent decline in cases of *N. meningitidis* can be attributed to delaying diagnostic lumbar puncture in children with clinically obvious meningococcal disease. Antibiotic pre-treatment may have resulted in an underestimation of CSF culture-positive meningococcal cases [10].
The high prevalence of *K. pneumoniae* meningitis can be explained by two nosocomial outbreaks of *K. pneumoniae* during the study period.

The decrease in *H. influenzae* meningitis can be attributed to the benefit derived from immunization, as observed in other studies [11]. The 3 months median age of children with *H. influenzae* meningitis is much younger than 9.3 to 20 months described in the literature [1, 3, 4, 11, 12]. This is attributable to protection of older children by the introduction of Hib vaccine at 6, 10 and 14 weeks of age in July 1999. *Streptococcus pneumoniae* has become the second commonest cause of acute bacterial meningitis with a percentage of cases remaining unchanged since the 1980s and 1990s [3, 4]. A similar reduction to *H. influenzae* is anticipated with introduction of PCV in 2009. In 2009, the South-African PCV vaccination rate was 10% for the third dose, increasing to 64% in 2010 [13]. Studies investigating the effect of vaccination in HIV-infected children are ongoing.

Bacille Calmette-Guerin vaccination at birth is part of the EPI schedule with coverage of >94% in 2009 [13]. Despite the evidence of this providing protection against disseminated and severe TB complications, we have documented this high incidence of TBM.

Aseptic meningitis remains the commonest type of meningitis. Primary health care provided at public clinics in the Western Cape have been guided by Integrated Management of Childhood Illness principles since 2000. These guidelines advocate administration of intramuscular ceftriaxone to all children with suspected serious bacterial infection before transfer to hospital [14]. This could have resulted in a reduction of culture-positive meningitis cases.

It may also further explain the reduced cases of meningococcal meningitis and why pneumococcal meningitis has not increased in the face of the HIV epidemic.

The study also found that many children with bacterial meningitis, TBM included, were not offered HIV testing. This represents a missed opportunity for early diagnosis of HIV-infected children, which would have allowed for early initiation of anti-retroviral treatment (ART). Very few neonates were HIV tested due to maternal HIV screening that occurred during pregnancy.

Despite using clear and accepted definitions to classify meningitis into categories and expert consensus, the retrospective nature of this study may have resulted in incorrect exclusion or classification of cases, such as partly treated bacterial meningitis, mistaken for aseptic meningitis. Diagnostic methods in the laboratory have changed since earlier studies, with bacterial latex agglutination test no longer being performed, while routine viral cultures of CSF were never performed. Episodes of viral meningitis were therefore most likely classified as aseptic meningitis, and some cases of bacterial meningitis were classified as septic.

### Conclusions and recommendations

The study confirms the efficacy of Hib vaccination. A similar favorable impact is anticipated with PCV. All health-care workers in resource-poor countries, especially Global Alliance for Vaccines and Immunization-eligible countries, should actively promote vaccination against preventable causes of meningitis ensuring correct supply and delivery methods for a functioning EPI schedule.

Primary health strategies must be improved for TB prevention, contact tracing and prophylaxis. Otherwise, it will be unlikely that the development goal of halving the 1990 TB prevalence and mortality rate by 2015 will be reached in the Western Cape [15]. Testing for HIV infection should be part of the diagnostic workup of any child presenting with bacterial meningitis or TBM in an area where HIV is endemic. This would allow for earlier diagnosis and initiation of anti-retroviral treatment.

### References


