Favorable Prognosis of Purulent Meningitis in Patients Infected with Human Immunodeficiency Virus

Benito Almirante, Mireia Saballs, Esteban Ribera, Carles Pigrau, Joan Gavalda, Isabel Gasser, and Albert Pahissa

We prospectively reviewed all cases of purulent meningitis among human immunodeficiency virus (HIV) type 1–infected patients >14 years old that occurred at the Hospital General Vall d’Hebron (Barcelona) during the period 1 January 1985 through 31 March 1997. There were 12 episodes of purulent meningitis in nine of 2,150 HIV-1-infected patients. The annual rate of purulent meningitis was 0.465 cases per 1,000 patients, a rate that is 150 times higher than that for the general population. During 10 episodes, CD4⁺ lymphocyte counts were <200/mm³. The etiologic organism was Streptococcus pneumoniae in nine episodes (seven episodes occurred in four splenectomized patients), and Escherichia coli, Streptococcus agalactiae, and Enterococcus faecium each caused one episode. Clinical features and cerebrospinal fluid abnormalities were similar to those observed among patients without HIV-1 infection. All patients had bacteremia. The overall mortality was 8.3%. We conclude that purulent meningitis, particularly pneumococcal meningitis, is more frequent among HIV-1-infected patients than in the general population. The prognosis for HIV-1-infected patients is better than for HIV-1-negative patients.

Patients infected with HIV-1 have a primary defect in cellular immunity. The majority of opportunistic infections (due to protozoa, fungi, mycobacteria, and viruses) that affect this population are attributed to this defect. It is also known, however, that dysfunction in humoral immunity and impaired monocyte/macrophage activity can occur in these patients, placing them at increased risk for bacterial infection [1, 2].

The characteristics of invasive pneumococcal disease in HIV-1-infected patients have been well described in the literature, but the incidence, etiology, and evolution of purulent meningitis are unknown. To date, there have been reports only of isolated cases. The aim of our study was to evaluate the clinical characteristics, etiology, and prognosis of purulent meningitis in a cohort of 2,150 HIV-1-infected patients treated at our hospital.

Patients and Methods

Hospital General Vall d’Hebron (Barcelona) is a 700-bed, tertiary care university hospital that serves as the referral center for a population of ~750,000 inhabitants. From January 1985 to March 1997, all adult patients (>14 years old) admitted for treatment of purulent meningitis were followed up prospectively. The clinical histories of those who had concomitant HIV infection when meningitis was diagnosed were then analyzed. During the same period, 2,150 cases of HIV infection were treated in our institution; 1,190 of these cases met the criteria for AIDS (only on the basis of clinical criteria described in the 1993 Centers for Disease Control and Prevention classification and not CD4⁺ lymphocyte counts). Twelve episodes of purulent meningitis were diagnosed in nine HIV-1-infected patients. The criteria for establishing a diagnosis of purulent meningitis were the presence of a clinical process consistent with the disease and isolation of a pathogenic microorganism in CSF samples. Gram stain and culture were performed on all CSF samples with use of standard methods. Before antibiotic treatment was initiated, two blood cultures were performed with the BACTEC 600 (Becton Dickinson, Mountain View, CA).

Streptococcus pneumoniae isolates were identified by standard techniques. All strains were tested for susceptibility to penicillin by means of disk diffusion in agar. The strains showing reduced susceptibility to penicillin were tested by agar diffusion for susceptibility to cefotaxime and vancomycin, according to the guidelines established by the National Committee for Clinical Laboratory Standards [3]. Conventional antibiotic susceptibility studies were performed according to the species for the remaining bacterial isolates (non-S. pneumoniae).

After obtaining CSF and blood samples for culture, antimicrobial treatment was administered on the basis of gram stain results. When gram-positive cocci were found, treatment with iv cefotaxime at dosages of 150–300 mg/(kg·d) or ceftriaxone at a dosage of 50 mg/(kg·d) was initiated. When a gram stain showed gram-negative cocci or bacilli, ceftriaxone was administered at a dosage of 50 mg/(kg·d). When no microorganisms were seen, broad-spectrum cephalosporin therapy, with or without ampicillin, was started. Patients with a severely altered consciousness received adjuvant dexamethasone therapy at a dosage of 0.05 mg/kg every 8 hours for 48–72 hours. For
patients with convulsions, diphenylhydantoin was given at an initial dosage of 18 mg/kg, followed by 2 mg/kg every 8 hours during the entire course of treatment for meningitis. All patients who survived the episodes of purulent meningitis were followed up on an outpatient basis until death or the end of the study (March 1997). Survival among the patients was evaluated by an actuarial life curve with use of the BMDP statistical software package (BMDP, West Los Angeles, CA).

Results

Between January 1985 and March 1997, 263 episodes of purulent meningitis were diagnosed in adults >14 years old at our center. The distribution by etiology, relationship with HIV-1 infection, and associated mortality are shown in Table 1. Twelve episodes occurred in nine HIV-1-infected patients (two women and seven men; mean [±SD] age, 36 ± 4 years), an annual rate of 0.465 cases per 1,000 patients. The remaining 251 episodes occurred in 235 patients (mean [±SD] age, 52 ± 12 years) without HIV-1 infection. The routes by which HIV-1 infection was transmitted were parenteral drug abuse (n = 5), transfusion of blood derivatives (n = 2), or heterosexual contact (n = 2). CD4⁺ lymphocyte counts were <200/mm³ during 10 episodes, 250/mm³ during one episode, and >500/mm³ during the last episode. Four patients met the criteria for AIDS during the episodes of meningitis. Eight of the episodes (six caused by pneumococci, one by Escherichia coli, and one by Enterococcus faecium) developed while the patients were receiving cotrimoxazole prophylaxis.

In addition to HIV-1 infection, all nine patients presented with underlying conditions that made them prone to bacterial infection: four had histories of splenectomy (one patient had three episodes of pneumococcal meningitis over a 4-year period [cases 2, 11, 12], and another had two episodes of pneumococcal meningitis in 2 years [cases 3 and 4]), four had cirrhosis of the liver, four were alcoholics, three were smokers, one had neutropenia (neutrophil count, <500/mm³), and one had chronic otitis media. One patient presented with E. faecium meningitis and catheter-related sepsis caused by the same etiologic agent.

Nine of the episodes of meningitis were due to S. pneumoniae (seven of the episodes in the four splenectomized patients), one was due to E. coli in a patient who was neutropenic secondary to chemotherapy for non-Hodgkin’s lymphoma, one was due to Streptococcus agalactiae in a patient with liver cirrhosis, and the last was due to E. faecium in a patient who had sepsis associated with a subclavian catheter that had been placed for maintenance treatment of cytomegalovirus retinitis.

All patients complained of headache, and the majority had fever (83%), vomiting (75%), and meningism (91%). At the time that meningitis was diagnosed, seven of the patients had altered consciousness, which was severe in two cases. Convulsions were observed in three cases. One of the splenectomized patients presented with pneumonia and septic shock in addition to meningitis; this patient died 6 days later.

Analysis of CSF samples yielded the following results: median glucose level, 10 mg/dL (range, 0–54 mg/dL); median protein level, 320 mg/dL (range, 33–731 mg/dL); and pleocytosis with a predominance of polymorphonuclear cells (median cell count, 764/mm³; range, 15–14,000/mm³). Only one patient had normal glucose and protein levels. Gram staining of CSF was positive in six cases, five of which were due to S. pneumoniae and one of which was due to E. coli. All episodes were accompanied by bacteremia.

The susceptibilities of the strains to antibiotics were as follows: one strain of S. pneumoniae was resistant to penicillin, and four strains were moderately resistant to penicillin. Of these four strains, two were also moderately resistant to the broad-spectrum cephalosporins (MIC of cefotaxime, 1 mg/L). Only three isolates were resistant to cotrimoxazole; two of these isolates were recovered from patients receiving long-term prophylaxis with this drug. S. agalactiae was susceptible to penicillin (MIC, <0.01 mg/L). E. coli was resistant to ampicillin and cotrimoxazole and susceptible to the broad-spectrum cephalosporins. The patient with E. coli meningitis was also receiving co-trimoxazole prophylaxis. E. faecium was resistant to penicillin (MIC, ≥16 mg/L) and to ampicillin (MIC, ≥32 mg/L) and susceptible to vancomycin.

Data on antimicrobial therapy, adjuvant therapy, outcome, and follow-up are shown in Table 2. The patients who received diphenylhydantoin as adjuvant therapy had convulsions when meningitis was diagnosed. The median duration of follow-up was 37.5 months (range, 1–94 months). Figure 1 shows an actuarial life curve; at 26 months of follow-up, 50% of the patients were alive.

Discussion

The estimated annual incidence of bacterial meningitis among the HIV-1-infected patients treated at our center during

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>HIV-1-infected patients</th>
<th>HIV-1-negative patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases (%)</td>
<td>No. of deaths (%)</td>
</tr>
<tr>
<td>Neisseria meningitidis</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>9 (75)</td>
<td>1 (11.1)</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Other microorganisms*</td>
<td>3 (25)</td>
<td>0</td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>12 (100)</td>
<td>1 (8.3)</td>
</tr>
</tbody>
</table>

* Enterococcus faecium (one patient), Escherichia coli (one), and Streptococcus agalactiae (one).
Table 2. Etiology, treatment, and outcome of purulent meningitis among HIV-1-infected patients at the Hospital Vall d’Hebron, Barcelona, 1985–1997.

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Etiology (serotype)</th>
<th>Initial iv treatment</th>
<th>Definitive iv treatment</th>
<th>Adjuvant therapy (duration in d)</th>
<th>Outcome</th>
<th>Status at end of follow-up (no. of mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><em>Streptococcus pneumoniae</em> (34)</td>
<td>Ceftriaxone</td>
<td>Ceftriaxone</td>
<td>Dexamethasone (2)</td>
<td>Cured</td>
<td>Alive (94)</td>
</tr>
<tr>
<td>2</td>
<td>S. pneumoniae (6)</td>
<td>Ceftriaxone</td>
<td>Ceftriaxone</td>
<td>None</td>
<td>Cured</td>
<td>Alive (62)</td>
</tr>
<tr>
<td>3</td>
<td>S. pneumoniae (14)</td>
<td>Cefotaxime</td>
<td>Cefotaxime</td>
<td>Dexamethasone (2)</td>
<td>Cured</td>
<td>Alive (62)</td>
</tr>
<tr>
<td>4</td>
<td>S. pneumoniae (18)</td>
<td>Ceftriaxone</td>
<td>Penicillin</td>
<td>Diphenylhidantoin (7)</td>
<td>Cured</td>
<td>Alive (53)</td>
</tr>
<tr>
<td>5</td>
<td>S. pneumoniae (14)</td>
<td>Cefotaxime</td>
<td>Cefotaxime</td>
<td>Dexamethasone (3)</td>
<td>Cured</td>
<td>Alive (23)</td>
</tr>
<tr>
<td>6</td>
<td>S. pneumoniae (7)</td>
<td>Ceftriaxone</td>
<td>Ceftriaxone</td>
<td>Dexamethasone (3), manitol (1)</td>
<td>Cured</td>
<td>Alive (23)</td>
</tr>
<tr>
<td>7</td>
<td>S. pneumoniae (23)</td>
<td>Ceftriaxone</td>
<td>Ceftriaxone</td>
<td>Diphenylhidantoin (6)</td>
<td>Died</td>
<td>Dead (3)</td>
</tr>
<tr>
<td>8</td>
<td><em>Streptococcus agalactiae</em></td>
<td>Cefotaxime</td>
<td>Ceftriaxone</td>
<td>Diphenylhidantoin (8), manitol (1)</td>
<td>Cured</td>
<td>Dead (23)</td>
</tr>
<tr>
<td>9</td>
<td>Escherichia coli</td>
<td>Ceftriaxone</td>
<td>Ceftriaxone</td>
<td>None</td>
<td>Cured</td>
<td>Alive (5)</td>
</tr>
<tr>
<td>10</td>
<td>Enterococcus faecium</td>
<td>Cefotaxime + ampicillin</td>
<td>Vancomycin</td>
<td>Dexamethasone (4)</td>
<td>Cured*</td>
<td>Dead (1)</td>
</tr>
<tr>
<td>11</td>
<td>S. pneumoniae (23)</td>
<td>Cefotaxime</td>
<td>Cefotaxime</td>
<td>None</td>
<td>Cured</td>
<td>Alive (2)</td>
</tr>
<tr>
<td>12</td>
<td>S. pneumoniae (23)</td>
<td>Cefotaxime</td>
<td>Cefotaxime</td>
<td>None</td>
<td>Cured</td>
<td>Dead (3)</td>
</tr>
</tbody>
</table>

* A CSF sample obtained after therapy showed no biological alterations, and no bacterial growth was observed in the culture.

The clinical characteristics of meningitis in the HIV-1-infected patients were similar to those observed in the general population, with altered consciousness in 64% of episodes and convulsions in 27%. In a recent series of pneumococcal meningitis cases in the general population, 74% of patients had altered consciousness when the infection was diagnosed, and 30% had convulsions at some point in the disease process [4].

Blood cultures were always positive for our HIV-1-infected patients with purulent meningitis. In the general population the rate of positive blood cultures in cases of pneumococcal meningitis is ~65% [18], and the percentage of positive blood cultures associated with other etiologies varies. It is still unknown why the incidence of bacteremia is high among HIV-1-infected patients; this finding is not only associated with meningitis but also with other infections [19].

The incidence of invasive bacterial infection is much higher among patients with HIV-1 infection than in the general population, and the frequency of bacteremia, particularly among patients with pneumococcal infection, is also higher. It has been estimated that the incidence of pneumococcal bacteremia among HIV-1-infected patients may be 100 times higher than in the general population [1]. In a study of HIV-1-infected patients with sickle cell anemia, the authors concluded that although this hematologic disease is a risk factor for pneumococcal infection, the incidence of pneumococcal infection increases notably when there is coexisting HIV-1 infection [20]. It has recently been reported that the risk of invasive infection by *S. agalactiae* is ~30 times greater for HIV-1-infected patients [21]. This high rate of bacterial infections and the large number of relapses [1] evidence the existence of an alteration...
in humoral immunity. Up to 57% of bacteremic episodes occur before the appearance of an opportunistic infection indicating AIDS. This fact suggests that a deficiency in humoral immunity can develop before a deficiency in cell-mediated immunity leads to an infection indicative of AIDS [1], whereas relapses are more evident in advanced phases of HIV-1 infection [22].

Anomalies in chemotaxis, in the Fc and C3 membrane receptor [23], that would give rise to decreases in phagocytosis [24, 25]; in myeloperoxidase activity [26] with associated decreases in bacterial lytic activity; and in antibody-mediated cytotoxic activity have been described among HIV-1-infected patients [27]. These alterations could account for the higher rate of bacterial infections, which are often bacteremic and result in more relapses, in this population. It is difficult, however, to attribute the high incidence of bacterial meningitis to these alterations, since each of our patients had some clear risk factor for meningitis [4, 18].

The distribution of the S. pneumoniae serotypes causing meningitis in our series was similar to that described previously for patients with invasive infection and did not differ from the distribution among HIV-1-negative patients [28]. In our series, all but one of the isolates was one of the 23 serotypes covered by the currently available vaccine, including those with resistance to the β-lactams.

Reduced susceptibility to penicillin was observed for 62.5% of the S. pneumoniae isolates, and 25% were moderately resistant to the broad-spectrum cephalosporins. These percentages are similar to those observed previously in an area with a high incidence of invasive disease caused by penicillin-resistant pneumococci [29]. Recently, we confirmed that 25% of the pneumococci that caused invasive disease and were resistant to the broad-spectrum cephalosporins had been isolated from patients with HIV-1 infection [30]. On the basis of this high incidence, it has been speculated that there may be clonal dissemination among HIV-1-infected patients. Moreover, it has been recommended that any young patient with invasive infection caused by penicillin-resistant pneumococci be tested for antibodies to HIV-1 [28].

Empirical treatment of acute purulent meningitis is based on gram stain results. In our series, gram staining showed organisms in 50% of the cases. Given the high prevalence of β-lactam-resistant pneumococci in Spain, the presence of gram-positive cocci or gram-negative bacilli requires treatment with a broad-spectrum cephalosporin such as iv ceftaxime at dosages of 150–300 mg/(kg · d) [30, 31]. If no organisms are visible on a gram stain, iv ampicillin at a dosage of 2 g every 4 hours should be combined with ceftaxime so that the antimicrobial spectrum will include Listeria monocytogenes, especially in patients who are not receiving co-trimoxazole prophylaxis.

The outcome for our patients was satisfactory. The mortality was 8.3% in the acute phase, a figure that agrees with data in the literature [1, 32–34] and contrasts with the 18% mortality we found in the HIV-1-negative population [4]. It is difficult to explain the lower death rate among HIV-1-infected patients, who had other underlying conditions. Splenectomy, in particular, has been associated with high rates of death due to bacterial infection [35]. For HIV-1-infected patients with other bacterial infections such as bacteremic pneumonia, the related mortality is not greater than that for patients of the same age who do not have HIV infection [19]. It may be that a reduced immunologic response due to the immune deficit in HIV-1-infected patients spares the brain from the inflammatory alterations that are produced in the initial phases of meningitis and are directly related to mortality.

Acknowledgment

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References


