Tuberculous Meningitis in Adults: Review of 48 Cases

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The cases of 48 adult patients with tuberculous meningitis who were admitted to an intensive care unit (ICU) between 1982 and 1993 were reviewed. An underlying disease was present in 24 patients (50%), including 10 with human immunodeficiency virus infection. Forty-seven patients were referred to the ICU because of neurological deterioration; 22 were comatose at admission. Forty-six patients received antituberculous treatment; 36 required mechanical ventilatory support, and 16 underwent neurosurgery. Thirty-one patients died within 4 months after admission, and the remaining 17 were alive at a 1-year follow-up. Univariate prognostic analysis selected three variables, all assessed at admission, associated with outcome: time to onset of treatment of ≥3 days (P = .003), coma (P = .006), and simplified acute physiology score of >11 (P = .03). Thus, the outcome of tuberculous meningitis is mainly determined by the clinical stage at admission and the delay in starting treatment. These findings underscore the need to initiate early therapy as soon as the diagnosis of tuberculous meningitis is suspected.

Although tuberculous meningitis accounts for a small percentage of all the cases of tuberculosis in developed countries, it remains a serious problem for the physician because of the difficulty in making an early diagnosis and the severe consequences of delaying treatment. The recent report of an increase in the incidence of tuberculosis in developed countries, mainly among patients with low socioeconomic status or HIV infection, could lead to an increase in the number of cases of tuberculous meningitis [1]. Several series presenting the current features of tuberculous meningitis in adults in developed countries have been published in the last decade [2–7]. However, it is not known whether the routine use of CT, the spreading of HIV infection, or the accessibility of patients to intensive care support has modified the management and the course of this infection.

We reviewed the experience of our infectious diseases intensive care unit (ICU) to define the current clinical presentation and prognosis of adult patients with advanced stages of tuberculous meningitis.

Patients and Methods

Patients

The medical charts of all consecutive patients admitted to our infectious diseases ICU because of tuberculous meningitis between January 1982 and December 1993 were reviewed. Patients were included in the study if the diagnosis of tuberculous meningitis was established according to the following criteria: the isolation of Mycobacterium tuberculosis from the CSF, the presence of acid-fast bacilli revealed by direct examination of CSF or histologic examination of a meningeal specimen, and/or a CSF abnormality suggesting tuberculous meningitis that was demonstrated by the isolation of M. tuberculosis from extrameningeal tissue or the presence of acid-fast bacilli on extrameningeal tissue.

Medical history, clinical presentation at admission and during the stay in the ICU, and CSF, radiological and biological data for all the patients fulfilling the selection criteria were reviewed. The patient’s neurological status at the time of admission to the ICU was classified by using the Glasgow coma score (GCS), and the staging of tuberculous meningitis was established by the Medical Research Council (MRC) [8]. In stage 1, patients were fully conscious and rational and did not have focal neurological signs. In stage 2, patients were confused but not comatose or had neurological signs of localization such as hemiparesis or a single cranial nerve palsy. In stage 3, patients were comatose or stuporous or had multiple cranial nerve palsies or complete hemiplegia or paraplegia. Coma was defined as a GCS of ≤8 [9].

The clinical severity of the patients’ conditions at the time of admission to the ICU was established according to the simplified acute physiology score (SAPS) [10]. The outcomes after the patients were discharged from the ICU were obtained through medical charts and/or telephone calls to the patients or their primary care physician.

Statistics

Overall survival after admission to the ICU was estimated by the Kaplan-Meier product limit method. Univariate analysis
of prognosis was based on the $\chi^2$ test and Fisher's exact test. Levels of significance were represented by $P$ values derived from two-sided tests. A $P$ value of $\leq 0.05$ was considered to indicate a statistical difference.

Results

Main Characteristics of the Study Population

Fifty-one patients met the selection criteria; three of these patients were not included in the study because their medical charts were not available. The diagnosis of tuberculous meningitis was established by isolation of M. tuberculosis from CSF (38 patients), direct examination of the CSF smear (3), histologic examination of a tuberculoma requiring neurosurgery (1), necropsy (1), and demonstration of the microorganism in only an extraneurological specimen (5).

Nineteen patients were referred to the ICU by medical wards in our hospital, and 29 were referred by other institutions. At the time of admission, 12 patients for whom the diagnosis of tuberculous meningitis was established or presumed had been receiving antituberculous treatment for 1 to 3 days (5), 4 to 6 days (5), and 28 days (2).

Thirty-two patients underwent serological testing for HIV infection; 10 were found to be positive. Of the 16 patients who were not tested, all had been hospitalized before 1986, and no risk factor for HIV infection or suggestive medical history was found. From 1981 to 1986, one of 17 patients admitted because of tuberculous meningitis was HIV-infected, while nine of 31 patients admitted between 1987 and 1993 were HIV-infected.

The patients' ages ranged from 18 to 83 years (mean, 46 years). There were 32 males and 16 females. Most of the patients originated from France or Europe (23) and Maghreb or the Middle East (14), and the remaining were from Africa (4), Asia (4), and Haiti (3). An underlying disease or HIV infection was found in 24 patients (50%). Underlying medical conditions included alcoholism (5 patients), neoplasia (3), chronic renal failure, chronic respiratory disease (2), chronic cardiac disease (2), cirrhosis (1), psychiatric disease requiring institutionalization (1), and corticosteroid treatment (1). Of the HIV-infected patients, 3 were intravenous drug users, 2 were homosexuals, 4 were from central Africa or Haiti, and 1 had undergone multiple transfusions.

The distribution of the demographic characteristics was influenced by age. HIV infection was found mainly in patients younger than 40 years of age (seven cases). The sex ratio tended to 1 among patients older than 60 years of age, while there was an overrepresentation of male patients in the other patient age groups. An underlying condition, including HIV infection, was identified in 50% of patients in each patient age group.

Clinical Data

The cause of admission to the ICU was the worsening of neurological status in 47 patients and acute renal failure in one patient. Twenty-two patients (46%) were comatose at admission. Thirteen patients required mechanical ventilatory support within 48 hours of admission. By means of the MRC staging, 8 patients were classified as stage 1; 11, as stage 2; and 29, as stage 3. Stage 1 patients had a GCS of 14 or 15, stage 2 patients had GCSs ranging from 11 to 13, and all stage 3 patients had a GCS of $\leq 10$. The mean SAPS $\pm$ SD was 10.8 $\pm$ 5; 16 patients presented with a score of $>12$.

Thirty-one patients (65%) presented with fever, and seven (15%) presented with hypothermia; 10 had a body temperature between 36°C and 38°C. Meningeal stiffness was found in 42 cases (88%). Seizures and neurological signs of localization were present at the time of admission in eight patients (17%) and 25 patients (52%), respectively. Various degrees of hemiplegia, monoplegia, or paraplegia were found in 16 patients. A cranial nerve palsy was found in 15 patients. Eight patients presented with both hemiplegia or monoplegia and a cranial nerve palsy. Three additional patients presented with a cerebellar syndrome, which was associated with a cranial nerve palsy in two cases. One patient presented with a central facial palsy. Funduscopic examination showed a bilateral papilledema and choroidal tubercles in three patients and one patient, respectively.

Of the 12 patients who were already receiving antituberculous treatment, 11 were referred to the ICU because of neurological deterioration, and one was referred to the ICU because of acute renal failure. A clear cause of neurological deterioration could be found in four patients (ventricular dilation in three and severe hyponatremia in one). In the seven remaining patients, several mixed factors were involved, namely, hyponatremia, moderate ventricular dilation, occurrence of ischemic lesions, and bacterial pneumonia.

The CD4 lymphocyte count within the 2 months preceding admission was available for eight HIV-infected patients. The mean count $\pm$ SD was 154 $\pm$ 89/mm$^3$ (range, 28–336/mm$^3$). A previous AIDS-defining illness was found in five patients (tuberculosis, 3; Pneumocystis carinii pneumonia, 1; and wasting syndrome, 1). In the five remaining patients, the episode of tuberculous meningitis revealed the retrovirus infection. The results of the neurological evaluations (MRC staging, GCS, and physical findings) of HIV-infected patients did not differ from those of the neurological evaluations of patients without HIV infection (data not shown).

CSF and Laboratory Data

The results of examination of CSF obtained from lumbar punctures performed during the initial hospital admission and the ICU admission did not differ significantly (data not shown). During admission to the ICU, a lymphocytic predominance was observed in 72% of the patients (table 1). Examination of CSF obtained from the subsequent lumbar punctures of the 13 patients without lymphocytic predominance at the time of admission showed a switch to lymphocytic predominance (6),
a paucicellular fluid (2), and the same pattern (5). At admission, the CSF protein level in all patients was above normal (>3 g/L in 19 patients [40%]), and the CSF glucose level was normal (>2.3 mmol/L) in 14 patients (30%) (table 1). Characteristics of CSF obtained from initial lumbar punctures and from those at ICU admission did not differ according to the HIV status (data not shown).

For 36 cases, culture of CSF from lumbar puncture was positive; among these cases, 35 were available for analysis of initial and subsequent lumbar punctures. *M. tuberculosis* was first isolated from CSF from the first lumbar puncture in 30 (86%) of 35 cases, from CSF from the second lumbar puncture in 4 (11%) of 35, and from CSF from the third lumbar puncture in one (3%) of 35. Direct examination of the CSF smear was positive in only six cases, including 2 cases with CSF from the first lumbar puncture, 2 with CSF from the second lumbar puncture, 1 with CSF from the third lumbar puncture, and 1 with CSF from the sixth lumbar puncture. All three patients for whom direct examination of the CSF smear was positive and culture of CSF was negative had been receiving antituberculous therapy before CSF examination.

Fifteen patients had a prosthetic device placed for the treatment of hydrocephalus; the results of microbiological studies of ventricular CSF were available in 12 of these cases. Culture and direct examination of ventricular CSF were positive in six and five cases, respectively; both the culture and the direct examination were positive for three patients. The direct examination of ventricular CSF was positive for four patients for whom the direct examination of CSF obtained by lumbar puncture was negative.

The sensitivity of the isolates was available in 27 cases; the isolates were resistant to streptomycin in two cases, and in the remaining cases, the isolates were sensitive to all the other drugs tested (isoniazid, rifampin, pyrazinamide, and ethambutol).

The sodium level in plasma was <135 mmol/L in 42 patients. Hypernatremia (defined by a plasma sodium level of >145 mmol/L) was observed in three patients; it was due to excessive correction of dilutional hyponatremia in one patient and to diabetes insipidus in two patients.

### Neuroradiological Data

The results of CTs of 47 patients during admission are shown in table 2. The commonest finding was ventricular dilation, observed in 24 patients (51%). Basilar and superficial meningeal enhancements were found in 18 patients (38%) and 17 patients (36%), respectively. Six patients (five in stage 3 and one in stage 2) presented with hypodensities consistent with cerebral infarcts that correlated to clinical findings for all of them but one. Ring or nodular enhancing lesions were present in five patients. In three of these patients, no symptoms could be attributed to these lesions, including >10 disseminated centimetric lesions in 1 patient, a 1-cm cerebellar lesion in 1, and a 2-cm lesion in the right frontal lobe in 1. In the two remaining patients, these lesions were symptomatic; in one case, a 3-cm cerebellar lesion was associated with severe intracranial hypertension, and in the other case, a hypothalamic lesion was responsible for behavioral troubles. None of the HIV-infected patients presented with a ring or nodular enhancing lesion at admission to the ICU.

Subsequent CTs were obtained throughout the hospitalization according to clinical indication (table 2); the development of ventricular dilation and cerebral infarcts were shown in six and nine additional patients, respectively. Ring or nodular enhancing lesions developed in eight patients, of whom four were HIV-infected. The tuberculomatous nature of these lesions in the other four patients was proven by necropsy in 1, was highly probable (as suggested by a good outcome with antituberculous treatment alone at a 1-year follow-up) in 1, and was unproven (refusal and failure of brain biopsy) in 2.

### Extraneurological Tuberculous Localizations

An extraneurological tuberculous localization in 32 patients was diagnosed either before or during hospitalization in the

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**Table 1.** Findings of examinations of CSF obtained from lumbar punctures during admission to the ICU of 47 patients with tuberculous meningitis.

<table>
<thead>
<tr>
<th>Finding</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC count (×10⁶/L)</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>273 ± 722</td>
</tr>
<tr>
<td>Range</td>
<td>3 – 5000</td>
</tr>
<tr>
<td>No. with indicated count</td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>2</td>
</tr>
<tr>
<td>5 – 50</td>
<td>9</td>
</tr>
<tr>
<td>51 – 100</td>
<td>32</td>
</tr>
<tr>
<td>101 – 1,000</td>
<td>3</td>
</tr>
<tr>
<td>&gt;1,000</td>
<td>1</td>
</tr>
<tr>
<td>No. with lymphocyte count (%)</td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>13</td>
</tr>
<tr>
<td>&gt;50</td>
<td>34</td>
</tr>
<tr>
<td>Protein level (mg/L)</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>3.45 ± 2.86</td>
</tr>
<tr>
<td>Range</td>
<td>0.6 – 15.1</td>
</tr>
<tr>
<td>No. with indicated level</td>
<td></td>
</tr>
<tr>
<td>0.6 – 2</td>
<td>19</td>
</tr>
<tr>
<td>2.1 – 3</td>
<td>9</td>
</tr>
<tr>
<td>3.1 – 5</td>
<td>11</td>
</tr>
<tr>
<td>&gt;5</td>
<td>8</td>
</tr>
<tr>
<td>Glucose level (mmol/L)</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>1.9 ± 1.3</td>
</tr>
<tr>
<td>Range</td>
<td>0.1 – 5.3</td>
</tr>
<tr>
<td>No. with indicated level</td>
<td></td>
</tr>
<tr>
<td>0 – 1.0</td>
<td>16</td>
</tr>
<tr>
<td>1.1 – 2.2</td>
<td>17</td>
</tr>
<tr>
<td>2.3 – 3.4</td>
<td>9</td>
</tr>
<tr>
<td>&gt;3.4</td>
<td>5</td>
</tr>
</tbody>
</table>

*NOTE.* One patient, who underwent neurosurgery during admission, did not undergo lumbar puncture. ICU = intensive care unit.
Table 2. Findings of CTs of 47 patients with tuberculous meningitis during admission and throughout hospitalization.

<table>
<thead>
<tr>
<th>Neuroradiological finding</th>
<th>Admission CTs per MRC stage* at ICU admission</th>
<th>All CTs per MRC stage* at ICU admission</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 (n = 8) 2 (n = 10) 3 (n = 29) Total</td>
<td>1 (n = 8) 2 (n = 10) 3 (n = 29) Total</td>
</tr>
<tr>
<td>Ventricular dilation</td>
<td>3 5 16 24</td>
<td>4 8 18 30</td>
</tr>
<tr>
<td>Cerebral infarct</td>
<td>0 1 5 6</td>
<td>1 3 11 15</td>
</tr>
<tr>
<td>Basilar enhancement</td>
<td>4 5 9 18</td>
<td>5 7 16 28</td>
</tr>
<tr>
<td>Supertificial meningeal enhancement</td>
<td>2 5 10 17</td>
<td>5 7 15 27</td>
</tr>
<tr>
<td>Ring or nodular enhancing lesion</td>
<td>3 2 0 5</td>
<td>5 4 4 13</td>
</tr>
<tr>
<td>No abnormality</td>
<td>3 2 5 10</td>
<td>2 1 2 5</td>
</tr>
</tbody>
</table>

NOTE. ICU = intensive care unit; MRC = Medical Research Council.
* See text for definition of MRC stages.

At admission to the ICU, 11 patients (23%) had a previously diagnosed extraneurological tuberculous localization (table 3). The diagnosis was made 2 to 4 months before admission for four patients whose compliance with treatment was poor; three of these patients had concomitant HIV infection. For the seven remaining patients, the diagnosis was made within 10 days before admission.

In 46 cases, a chest roentgenogram obtained during admission was available for study. These films showed a miliary pattern in 6 patients, lesions consistent with past or active pulmonary tuberculosis in 14, nontuberculous lesions in 3 (bi-

Table 3. Extraneurological tuberculous localizations in 48 patients with tuberculous meningitis.

<table>
<thead>
<tr>
<th>Time of diagnosis, localization</th>
<th>HIV-positive patients (n = 10)</th>
<th>HIV-negative patients (n = 38)</th>
<th>All patients (n = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission to the ICU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any extraneurological involvement</td>
<td>3 8 11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary tuberculosis</td>
<td>2 5 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary and/or genital tuberculosis</td>
<td>1 1 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph node tuberculosis</td>
<td>3 0 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appendicular tuberculosis</td>
<td>0 1 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pott’s disease</td>
<td>0 1 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU hospitalization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any extraneurological involvement</td>
<td>4 17 21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary tuberculosis</td>
<td>2 15 17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary and/or genital tuberculosis</td>
<td>0 4 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph node tuberculosis</td>
<td>2 1 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granulomatous hepatitis</td>
<td>1 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any time during hospitalization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any extraneurological involvement</td>
<td>7 25 32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary tuberculosis</td>
<td>4 20 24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary and/or genital tuberculosis</td>
<td>1 6 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph node tuberculosis*</td>
<td>5 1 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granulomatous hepatitis</td>
<td>1 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appendicular tuberculosis</td>
<td>0 1 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pott’s disease</td>
<td>0 1 1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE. ICU = intensive care unit.
* Significant difference between HIV-positive and HIV-negative patients (P < .001; Fisher’s exact test).
lateral alveolar pneumonia in 1 and right inferior aspiration pneumonia in 2), and no abnormalities in 23.

Treatment

Two patients did not receive antituberculous treatment. An HIV-infected patient who presented with lymphocytic meningitis and for whom a CSF culture was positive for \textit{Nocardioid asteroides} died; autopsy and postmortem growth from CSF samples revealed disseminated tuberculosis with meningeal involvement. Another institutionalized psychiatric patient who presented with an unexplained increase in the rate of seizure episodes was admitted to the hospital because of severe multiorgan failure and died in 24 hours; autopsy demonstrated disseminated tuberculosis with meningitis.

The remaining 46 patients received therapy with a combination of isoniazid and rifampin and ethambutol and streptomycin (5), ethambutol and pyrazinamide (29), ethambutol alone (10), and amikacin alone (2). Fifteen patients were treated concomitantly for a cerebral pyogenic abscess or listeriosis until confirmation of tuberculosis meningitis. During hospitalization in the ICU, adverse effects (cytolytic hepatitis) leading to definitive interruption of treatment with isoniazid (three cases) and pyrazinamide (five cases) were observed. Treatment with both drugs had to be definitively interrupted in one patient. Steroid treatment was given to 31 patients. The reasons for not giving steroids therapy to the remaining patients were stage 1 illness (4 cases) and uncertain diagnosis of tuberculosis and eventual mortality of other pathogens (11).

The mean delay ± SD between the initial hospitalization (whether in the ICU) for tuberculosis meningitis and the start of antituberculosis treatment (referred to as time to onset of treatment) could be accurately measured for 38 patients as 6.3 ± 6.7 days. This delay was ≥3 days for 23 patients and 7 days for 11 patients.

A total of 36 patients needed mechanical ventilatory support for a mean time ± SD of 29 ± 29 days (range, 1 – 120 days). The neurological status was the main reason for ventilatory support in all patients. In eight patients, there was evidence of an additional respiratory pathological condition leading to mechanical ventilation: milroy disease or extensive tuberculous pneumonia (5), aspiration pneumonia (1), bacterial pneumonia (1), and silicosis (1).

Sixteen patients underwent neurosurgery. In one patient, a 3-cm cerebellar tuberculoma associated with severe intracranial hypertension was excised. A CNS prosthetic device was placed in the 15 remaining patients because of deterioration of the neurological status associated with ventricular dilation on the CT. In 14 cases, this procedure was performed within 7 days of admission to the ICU. The mean duration ± SD of drainage was 34 ± 33 days (range, 7 – 115 days). Infection of the ventricular device was observed in three patients; \textit{Staphylococcus epidermidis} (2 patients), \textit{Pseudomonas aeruginosa} (1), and \textit{Enterococcus faecalis} (1) were the causative organisms.

Outcome

The mean duration ± SD of hospitalization in the ICU was 33 ± 34 days. The mortality rate in the ICU was 50% (24 of 48). Death could be directly attributed to neurological deterioration (20 patients), nosocomial pneumonia (1), septic shock (1), and multiorgan failure (2). In five patients, additional factors could have contributed to neurological deterioration: infection of the ventricular device (2), severe variations in natremia due to inappropriate secretion of antidiuretic hormone followed by diabetes insipidus (1), and sequelae of cardiorespiratory arrest (2). Nosocomial infections in 21 patients were diagnosed during hospitalization in the ICU. The frequency of nosocomial infection was significantly higher among patients who received steroid therapy than among those who did not (18 of 31 vs. 3 of 17, respectively; \(P < .02\); Fisher's exact test). Opportunistic infections (cryptosporidiosis, cytomegalovirus polyradiculo-neuropathy, and disseminated cytomegalovirus infection, respectively) developed in three HIV-infected patients during hospitalization in the ICU.

After discharge from the ICU, seven additional deaths occurred, all within 120 days of admission to the ICU. Three of these patients were HIV-infected and died of neurological deterioration that was poorly investigated. The compliance with antituberculous treatment was poor in two of these patients. The four non-HIV-infected patients were 83, 83, 77, and 49 years old, respectively, and died as a consequence of bedridden status. The 17 remaining patients were still alive 12 months after admission to the ICU; four had neurological sequelae (hemiparesis, 1; diplopia, 1; static cerebellar syndrome, 1; and psychiatric disturbances, 1). The overall 120-day mortality rate was estimated at 65% (95% CI, 51.5 – 78.5; median time of death, 64 days).

Of the 15 patients who underwent neurosurgery for treatment of hydrocephalus, four (27%) were still alive at 12 months, one of whom had severe sequelae. These four patients (two in stage 2 and two in stage 3 at admission to the ICU) had undergone placement of an external ventricular drainage device (3) and a Rickham reservoir (1) for a duration of 10 – 16 days. Repeated CTs throughout the hospitalization showed isolated ventricular dilation in these four patients, while associated signs of cerebral infarcts were found in nine of the 11 patients who died.

Among the variables assessed within 48 hours of ICU admission, time to onset of treatment of ≥3 days (\(P = .003\)), coma (\(P = .006\)), and a SAPS of >11 (\(P = .03\)) were significantly associated with death at 4 months. Clinical presentation and laboratory and neuroradiological data had no significant effect on outcome.

Discussion

Recent series from developed countries [2, 4 – 6, 11] have demonstrated that tuberculous meningitis remains a serious problem. However, most of these studies included pediatric...
patients and are not homogeneous for the antituberculous regi-
men or the access to CT. Advanced stages of the disease repre-
sent a small proportion of the cases, and few data are available
on the results of neurosurgery and the management of such
advanced cases in the ICU. Our study provides data for 48
adult patients admitted to an infectious diseases ICU because
of severe tuberculous meningitis. During our 12-year study
period, antituberculous treatment, indications for steroid ther-
apy, availability of CT, and neurosurgical expertise were simi-
lar for all patients.

Our overall mortality rate was 65%; all deaths occurred in
the first 4 months after admission. Neurological sequelae
were present in four of the 17 patients who were alive at 1 year,
and the mortality rate among stage 2 and stage 3 patients was
55% (six of 11) and 83% (24 of 29), respectively. In recent
studies [5, 6, 12–16], the mortality rates ranged from 4% to
24% among stage 2 patients and from 37% to 87% among
stage 3 patients. The high proportion of patients with stage 3
disease (29 of 48) and the selection bias of an ICU-referred
population may explain the severe outcome for our patients.

Patients were referred to the ICU for neurological reasons
in nearly all cases (47 of 48). Several factors may contribute
to the worsening of neurological status, including raised intra-
cranial pressure, development of ischemic lesions, hypona-
tremia, decompensation of an underlying disease, and severe
nosocomial infection. Although the role of any of these factors
could be demonstrated in individual cases, multiple mecha-
nisms were simultaneously involved in most of our patients.
Of 11 patients admitted because of neurological deterioration
while receiving antituberculous treatment, four had hypona-
tremia and hydrocephalus that were obviously responsible for
the worsening of their neurological status.

Antituberculous treatment had not been started at the time
of referral to the ICU in 36 cases, thus underscoring the diffi-
culty in establishing the diagnosis of tuberculous meningitis.
In most instances, the diagnosis is presumptive and relies on
the clinical presentation and the results of CSF and neuroradio-
logical studies.

The direct examination of repeated large-volume CSF speci-
mens would be the simplest way to obtain a rapid diagnosis.
Direct examination of smears of CSF from lumbar punctures
was positive for 12.5% (6) of 48 patients, a rate that is relatively
low compared with rates of 37% to 87% found in other series
[5, 13]. We observed positive direct examinations of ventricular
CSF samples from four patients whose direct examinations of
CSF from lumbar punctures were negative. The positivity of
direct examination of ventricular CSF smears alone has been
described by other investigators [17] and may be related to a
larger volume of CSF obtained from ventricular drainage than
from lumbar puncture.

The contribution of extrameningeal tuberculous infection in
establishing a reliable presumptive diagnosis must be empha-
sized. Tuberculous meningitis in adults is frequently secondary
to or associated with reactivation of tuberculosis in extramenin-
gal foci. Sixty-six percent of patients in this series had a
proven extrameningeal tuberculous localization, a rate that is
relatively higher than rates of 40% to 45% reported in recent
studies of tuberculous meningitis in adults [2, 3, 5]. As ob-
served by other researchers [11], lymph node tuberculosis was
more frequent in HIV-infected patients.

In agreement with other reports [11, 18], we found that the
clinical features and the CSF profiles of tuberculous meningitis
were not modified in HIV-infected patients. Of note, as ob-
served in previous studies, the development of tuberculous
meningitis in noncompliant patients treated for tuberculosis
elsewhere [11, 19] and the occurrence of concomitant CNS
infections [19, 20] were not uncommon in HIV-infected pa-
ients.

Although CT abnormalities are not specific, their association
with CSF and clinical findings may suggest the diagnosis of
tuberculous meningitis [6, 21–23]. Hydrocephalus and basilar
enhancement were present at the time of admission in 50% and
36% of patients, respectively, and throughout hospitaliza-
tion, only 10% of patients had a normal CT. No association
was found between CT findings and outcome. In fact, such
abnormalities are rare as a single finding, and their contribu-
tion to the neurological status is difficult to evaluate.

Ventriculoperitoneal or ventriculoatrial shunting is the most
widely used method to treat hydrocephalus complicating tuber-
culous meningitis [17, 24–27]. In this study, external ventricu-
lar drainage devices or reservoirs were inserted in all patients.
Three (20%) of 15 patients who underwent neurosurgical treat-
ment of hydrocephalus were alive without sequelae at 1 year.
In patients whose conditions did not improve, additional cerebral
lesions probably contributed to neurological deterioration.

CT studies of the subset of patients who underwent neurosur-
gical treatment of hydrocephalus found that nine of 11 patients
who died had evidence of cerebral infarcts compared with none
of the four patients who were still alive at 1 year. Intracranial
pressure monitoring has only been evaluated for children, and
its use remains limited [28]. In 114 patients (61 of whom were
>10 years old) who underwent shunt surgery, the stage of
disease at admission was the only variable correlated with out-
come [27]. The age, the CSF characteristics, and the need for
bilateral shunting had no prognostic significance. It now seems
reasonable to propose early ventricular drainage for any patient
whose neurological condition deteriorates or fails to improve
in spite of antituberculous treatment and whose CT reveals
ventricular dilation.

Although the use of steroids for treatment of tuberculous
meningitis is still debated [12, 15, 29], most investigators agree
that patients presenting with severe disease may have some
benefit from steroid treatment [30]. In this retrospective study,
it was not possible to assess the effect of steroid treatment. We
found a correlation between steroid treatment and nosocomial
infection, which may not be a causal relationship and may
reflect a longer stay in the ICU and a higher rate of invasive
procedures.
As found by other researchers [5, 6, 8, 13], we identified the delay to onset of treatment and the neurological status at admission as the main clinical prognostic factors. Because the time to onset of treatment could be accurately determined for only 38 patients, multivariate analysis was not performed. Other reported prognostic factors of tuberculous meningitis include the stage at the time of onset of antituberculous treatment, extreme ages, associated chronic medical disease, CSF protein level of >3 g/L, and CT changes [3, 6, 13, 31].

The management of tuberculous meningitis in the ICU allows careful monitoring of the clinical status of a patient so that decisions about ventilatory support, CT evaluation, and neurosurgical intervention can be rapidly made. Although the ICU was beneficial for several patients, the overall mortality rate associated with advanced stages of tuberculous meningitis remains high, mainly because of a high rate of undiagnosed cases at admission. This fact emphasizes the view that improving the diagnosis of tuberculous meningitis depends on the ability of physicians to establish the diagnosis rapidly and to start treatment at an early stage.

References