Pathophysiology and Prognosis in Vietnamese Adults with Tuberculous Meningitis

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The pathogenesis of tuberculous meningitis remains unclear, and there are few data describing the kinetics of the immune response during the course of its treatment. We measured concentrations of pro- and anti-inflammatory cytokines in serial blood and cerebrospinal fluid (CSF) samples from 21 adults who were being treated for tuberculous meningitis. CSF concentrations of soluble tumor necrosis factor–α receptors and of matrix metalloprotein–9 and its tissue inhibitor were also measured, and blood-brain barrier permeability was assessed by the albumin and IgG partition indices. CSF concentrations of lactate, interleukin-8, and interferon–γ were high before treatment and then decreased rapidly with antituberculosis chemotherapy. However, significant immune activation and blood-brain barrier dysfunction were still apparent after 60 days of treatment. Death was associated with high initial CSF concentrations of lactate, low numbers of white blood cells, in particular neutrophils, and low CSF glucose levels.

Tuberculous meningitis (TBM) is the most dangerous form of infection with Mycobacterium tuberculosis. Despite modern chemotherapy, it is fatal in 25% of adults and causes neurological sequelae in 25% of survivors [1]. However, the pathogenesis of this disease is unclear. An excessive intracerebral inflammatory response is considered to be responsible for the neurological damage, and adjunctive immunosuppression with corticosteroids has long been suggested as therapy, although the clinical benefit is uncertain [2]. Further understanding of the disease’s pathogenesis is required before more-specific therapies can be proposed.

Studies in rabbits have suggested that a central role exists for tumor necrosis factor (TNF)–α in the pathogenesis and progression of TBM [3]. Thalidomide, an inhibitor TNF-α production, reduced mortality in these models [4]. The mechanisms that underlie human disease have been less well studied. There are differences between the cytokines expressed in the cerebrospinal fluid (CSF) of patients with viral, bacterial, fungal, and tuberculous meningitides [5, 6]. High CSF concentrations of TNF-α have been observed repeatedly in untreated bacterial meningitis [5–7]. In contrast, the CSF concentrations reported in TBM are lower but may persist for longer [8]. The role of soluble TNF-α receptors in pathogenesis is uncertain. Higher TNF-α: receptor ratios in TBM than bacterial meningitis may reflect lower concentrations of biologically active TNF-α, which may prolong the inflammatory process [7]. TBM is also characterized by increased CSF expression of other proinflammatory cytokines, such as interferon (IFN)–γ, interleukin (IL)–1β, IL-8, and the anti-inflammatory cytokine IL-10 [9].

There is evidence of significant blood-brain barrier (BBB) breakdown in patients with TBM [10]. The mechanisms are probably multifactorial, although the matrix metalloproteinases (MMPs) have been recently implicated [11]. These molecules, which are secreted by monocytes and macrophages, are zinc-containing proteases that degrade extracellular matrix [12]. They may cause cerebral injury by disrupting the BBB, fa-
cilitating leukocyte migration, and cleaving myelin proteins. Elevated CSF MMP-9 concentrations have been associated with focal neurological deficit and death in Vietnamese adults with TBM [13]. The activity of the specific tissue inhibitors of MMPs (TIMPs) may be equally important, in particular the balance between MMP-9 and TIMP-1 (its specific inhibitor).

There are few studies that have described the expression of these molecules over the duration of treatment for TBM and their relationship with BBB dysfunction, clinical progression, and outcome after 9 months of antituberculosis chemotherapy (ATC). The purpose of the present study was to describe the effect of treatment on the constituents of the CSF—in particular the CSF expression of a range of pro- and anti-inflammatory molecules, MMP-9 and TIMP-1, and the integrity of the BBB—and to define which of the molecules carried prognostic significance.

PATIENTS AND METHODS

Setting. The adults in the study were admitted to the Clinical Research Unit at the Hospital for Tropical Diseases (HTD), Ho Chi Minh City, Vietnam. HTD is a 500-bed infectious-diseases hospital that serves the local community and acts as the tertiary referral center for infectious diseases in southern Vietnam. The HTD Scientific and Ethical Committee approved the study, and informed consent was obtained from all participants.

Patients. All adults not infected with human immunodeficiency virus (HIV) who were >15 years old and had received a diagnosis of TBM were eligible to enter the study. The severity of TBM at the start of treatment was graded according to a modified Medical Research Council criteria [14]: grade 1, a Glasgow coma score (GCS) of 15 out of 15, with no focal neurological signs; grade 2, GCS 11–14 or 15 but with focal neurological signs; and grade 3, GCS ≤ 10. All patients received streptomycin (20 mg/kg intramuscularly daily; maximum, 1 g) and an oral regimen of 5 mg/kg isoniazid, 10 mg/kg rifampicin, and 30 mg/kg pyrazinamide for 3 months, followed by 3 drugs (isoniazid, rifampicin, and pyrazinamide) for 6 months. None of the patients received corticosteroids. Clinical data were recorded prospectively in individual study notes.

Routine investigations. It is routine clinical practice in HTD for all patients with TBM to have a lumbar puncture at diagnosis (day 0) and on days 3, 7, 30, 60, and 270 of treatment. CSF cell counts and biochemistry results were obtained by use of standard methods for each sample. CSF lactate was only measured during the first 30 days of treatment. Routine microbiological investigation included microscopy of the centrifuged CSF deposit using standard methods for Ziehl-Neelsen, Gram’s, and Indian ink stains, with culture for fungi, pyogenic bacteria, and mycobacteria. The CSF supernatant from each sample submitted for microbiological analysis was stored at −70°C. Serum and plasma samples taken at the time of lumbar puncture were frozen at −70°C.

Laboratory methods. Commercial capture ELISA kits were used to measure CSF and blood concentrations of IFN-γ, TNF-α, IL-8, and IL-10 (OPTEIA ELISA; Becton Dickinson), and the CSF concentrations of MMP-9, TIMP-1, and the soluble TNF-α receptors 1 and 2 (TNF-αR1 and -R2; R&D systems). The lower limits of detection were 10 pg/mL IFN-γ, TNF-α, TNF-αR1, TNF-αR2, and IL-8; 15 pg/mL IL-10; 200 pg/mL TIMP-1; and 350 pg/mL MMP-9.

A commercial analyzer measured albumin and IgG concentrations in blood and CSF (Hitachi 917; Hitachi) by immunoturbimetry that used polyclonal anti-human albumin or IgG antibodies (Roche Diagnostics). The albumin index (AI) was calculated using the formula albuminCSF/albuminplasma. Normal ranges for albumin were 36–50 g/L in plasma and 0.16–0.36 g/L in CSF [15], and the normal range for AI is 0.0032–0.01. The formula used to calculate the IgG index (IgGI) was (IgGCSF × albuminplasma)/(albuminCSF × IgGplasma) [15]. The normal range for IgGI is 0.34–0.58 [15].

Statistical analysis. Normally distributed variables were compared by Student’s t test; all others were compared by the Mann-Whitney U test. The analysis of the correlation between variables was done by Spearman’s test. Variables associated by univariate analysis with death (P < .1) (table 1) were then incorporated into multivariate logistic regression. A forward stepwise variable-selection procedure was used with P-to-enter < .05 and P-to-remove > .1, to identify independent predictors of death. The analysis was done using SPSS software (version 10.0; SPSS).

RESULTS

Twenty-one adults consented to enter the study between October 2000 and April 2001. At the start of treatment, 8 were grade 1, 6 were grade 2, and 7 were grade 3. None of the adults had antibodies for HIV. A diagnosis of TBM was confirmed (acid alcohol-fast bacilli seen in the CSF or M. tuberculosis cultured from the CSF) in 15 (71%) of 21. One isolate was resistant to isoniazid, and the rest were sensitive to all first-line agents. The CSF was sterile in 12 (80%) of 15 confirmed cases by day 3 of ATC and in all 15 by day 7. A diagnosis of TBM was highly probable in the unconfirmed cases: brain computed tomography showed hydrocephalus and basal meningeal enhancement in 4 of 6 patients, 3 of whom had chest X-ray results consistent with active pulmonary tuberculosis. The remaining 2 adults were diagnosed with TBM on the basis of typical clinical and laboratory findings and response to treatment. The median length of symptoms before admission was 18 days (range, 6–45 days), and 5 (24%) of 21 patients died before completing treatment: 2 patients after 2 days, and the others...
Table 1. Cerebrospinal fluid (CSF) variables associated with death (*P* < .10).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survived (n = 16)</th>
<th>Died (n = 5)</th>
<th>95% CI</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF before treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total WCC, ×10⁶/mL</td>
<td>509 (289)</td>
<td>213 (284)</td>
<td>−7 to 599</td>
<td>.055</td>
</tr>
<tr>
<td>Lymphocytes, %</td>
<td>66 (21)</td>
<td>87 (13)</td>
<td>−42 to 1</td>
<td>.058</td>
</tr>
<tr>
<td>Neutrophils, %</td>
<td>31 (23)</td>
<td>13 (13)</td>
<td>−4 to 42</td>
<td>.098</td>
</tr>
<tr>
<td>Lactate, mmol/L</td>
<td>5.9 (2.6)</td>
<td>9.5 (3.3)</td>
<td>−6.8 to −0.4</td>
<td>.029</td>
</tr>
<tr>
<td>CSF:blood glucose</td>
<td>0.30 (0.11)</td>
<td>0.20 (0.11)</td>
<td>−0.007 to 0.2</td>
<td>.067</td>
</tr>
<tr>
<td>TIMP, ng/mL</td>
<td>433 (187)</td>
<td>674 (23)</td>
<td>−532 to 51</td>
<td>.098</td>
</tr>
<tr>
<td>Total neutrophils, median range, ×10⁶ cells/mL</td>
<td>108 (12–972)</td>
<td>3 (0–126)</td>
<td></td>
<td>.062</td>
</tr>
<tr>
<td>CSF, day 0–7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total WCC, ×10⁶ cells/mL</td>
<td>534 (388)</td>
<td>207 (262)</td>
<td>68–584</td>
<td>.014</td>
</tr>
<tr>
<td>Neutrophils, %</td>
<td>29 (22)</td>
<td>15 (15)</td>
<td>−0.1 to 29</td>
<td>.052</td>
</tr>
<tr>
<td>Lymphocytes, %</td>
<td>67 (22)</td>
<td>86 (15)</td>
<td>−33 to −4</td>
<td>.013</td>
</tr>
<tr>
<td>Total lymphocytes, ×10⁶ cells/mL</td>
<td>336 (276)</td>
<td>150 (180)</td>
<td>3–369</td>
<td>.047</td>
</tr>
<tr>
<td>Lactate, mmol/L</td>
<td>5.0 (2.1)</td>
<td>8.4 (3.1)</td>
<td>−5.3 to −1.4</td>
<td>.001</td>
</tr>
<tr>
<td>CSF:blood glucose</td>
<td>0.36 (0.12)</td>
<td>0.24 (0.09)</td>
<td>0.04–0.19</td>
<td>.003</td>
</tr>
<tr>
<td>Total neutrophils, median (range), ×10⁶ cells/mL</td>
<td>85 (0–1206)</td>
<td>6 (0–297)</td>
<td></td>
<td>.025</td>
</tr>
<tr>
<td>MMP-9, median (range), ng/mL</td>
<td>198 (0–395)</td>
<td>392 (0–784)</td>
<td></td>
<td>.058</td>
</tr>
</tbody>
</table>

**NOTE.** Data are mean (SD), except where noted. 95% confidence intervals (CIs) are shown for normally distributed variables.

*Not normally distributed: Mann-Whitney *U* test used.

after 13, 88, and 138 days of treatment. For the survivors, 2 (13%) of 16 had severe neurological sequelae after 9 months of ATC. The rest had a complete recovery by the end of treatment. There was no relationship between length of symptoms before admission and disease severity or outcome.

**Changes in CSF cellular and biochemical parameters over time.** The effect of ATC on CSF white blood cell count (WCC), protein, glucose, and lactate concentration is shown in figure 1. The mean WCC before treatment was 445 × 10⁶ cells/mL (SD, 308; range, 16–1200 cells/dL), at day 7 it was 533 × 10⁶ cells/mL (SD, 549; range, 1–1800 cells/dL), at day 30 it was 173 × 10⁶ cells/mL (SD, 213; range, 1–800 cells/dL), and at day 60 it was 48 × 10⁶ cells/mL (SD, 62; range, 1–160 cells/dL). The CSF WCC was elevated (>5 × 10⁶ cells/mL) in 8 (62%) of 13 samples taken after 270 days of ATC. CSF protein levels were elevated (>45 mg/dL) in many patients throughout the treatment period (figure 1B). The mean concentration at the start of treatment was 266 mg/dL (SD, 350; range, 66–1800 mg/dL) and was elevated in 5 (38%) of 13 patients at day 270. The CSF:blood glucose ratio was low (<0.5) in 23 (96%) of 24 measurements taken before the start of ATC (figure 1C). After 270 days of treatment, the ratio was normal in 15 (94%) of 16 patients. The mean CSF lactate concentration was 6.9 mmol/L (SD, 3.2; range, 2.4–14.0 mmol/L) before treatment, 4.7 mmol/L (SD, 1.6; range, 2.8–8.2 mmol/L) on day 2, 4.8 mmol/L (SD, 1.8; range, 1.5–7.2 mmol/L) on day 7, and 2.3 mmol/L (SD, 0.59; range, 1.7–3.1 mmol/L) on day 30. The CSF opening pressure was >20 cm H₂O in 12 of 24 measurements taken from 21 patients before the start of ATC, 6 (38%) of 16 measurements on day 7, 2 (14%) of 14 measurements on day 30, 1 (6%) of 16 measurements on day 60, and 0 of 13 measurements at the end of treatment. Two patients had CSF pressures >40 cm H₂O at the start of treatment, and both died.

**CSF and blood cytokines.** The CSF before treatment contained high concentrations of IL-8 (mean, 8297; SD, 9640; range, 430–41,298 pg/mL) and IFN-γ (mean, 708; SD, 887; range, 0–3156 pg/mL) (figure 2). CSF concentrations of TNF-α were lower (mean, 66; SD, 108; range, 0–412 pg/mL) and were undetectable in 15 (88%) of 17 adults at day 7 of treatment. In contrast, concentrations of TNF-α:γ1 and -r2 were easily detectable after 60 days of treatment, decreasing respectively to mean concentrations of 20 and 25 ng/mL at the end of treatment (figure 3C and 3D). Before treatment, the mean concentrations of TNF-γ1:TNF-α and TNF-α:γ2:TNF-α were 2.8 (0.24–11.5) and 7.7 (1.2–19.2), respectively (molar ratio, 8.2; SD, 10.9; range, 0.72–34.0 and molar ratio, 22.9; SD, 18.6; range, 3.5–56.8). These values increased to 9.9 (SD, 12.6; range, 1.9–24.4) and 18.1 (SD, 20.1; range, 3.9–41.2) by day 2, although only 3 patients had detectable concentrations of TNF-α at this time (molar ratio, 29.2; SD, 37.1; range, 5.7–72.0 and molar ratio, 53.6; SD, 59.5; range, 11.6–121.7). CSF concentrations of IL-10 decreased, with treatment, to undetectable concentrations at 9 months (mean, 2; range, 0–14 pg/mL) (figure 3A).
Figure 1. Mean values (with 95% confidence intervals) are shown of cerebrospinal fluid (CSF) total white blood cell counts (WCC), protein, and CSF:blood glucose over the treatment period. The continuous horizontal line represents the upper limit of the normal range. A, Total CSF WCC over the treatment period. B, Total CSF protein over the treatment period. C, CSF:blood glucose ratio over the treatment period. D, CSF lactate over the treatment period.

**CSF matrix metalloproteinases.** Figure 4 shows the mean CSF concentration of MMP-9 and TIMP-1 over the treatment duration. Before treatment, the mean CSF concentrations of MMP-9 and TIMP-1 were 146 ng/mL (SD, 186; range, 0–784 ng/mL) and 463 ng/mL (SD, 192; range, 83–754 ng/mL), respectively, which decreased with treatment to 70 ng/mL (SD, 139; range, 0–568 ng/mL) and 269 ng/mL (SD, 213; range, 53–701 ng/mL) by day 60.

**Albumin and IgG indices.** The albumin and IgG indices provide a useful measure of the extent of BBB permeability, and the serial values are presented in figure 5. There was evidence of breakdown in the BBB throughout the first 60 days of treatment. Only at 9 months were the means of both indices within the normal range.

**Prognosis.** Variables from those who died before the end of treatment were compared with those who survived (table...
Before treatment, only the CSF lactate concentration was significantly higher (P = .029) in those who died (95% confidence interval [CI] for the difference, 0.4–6.8 mmol/L). When all values from days 0–7 were included, the following were significantly associated with death: lower CSF WCC (95% CI, −68 to −584; P = .014), a higher percentage of lymphocytes in the CSF (95% CI, 4–33; P = .013), higher total CSF lymphocyte counts (95% CI, 3–369; P = .047), higher CSF lactate levels (95% CI, 1.4–5.3; P = .001), and a lower CSF glucose: blood ratio (95% CI, −0.04 to −0.19; P = .003). Lower total CSF neutrophil counts (P = .025), whose values were not normally distributed, were associated with death according to the Mann-Whitney U test.

Multivariate analysis was done to predict variables that were independently associated with death. The CSF lactate concentration was associated with death (odds ratio [OR], 1.6; 95%
CI, 0.97–2.64; \( P = 0.065 \)) before treatment, and CSF WCC (OR, 0.98; 95% CI, 0.97–0.99; \( P = 0.027 \)) was associated with death over the first 7 days of treatment.

The same analysis was done for patients who presented with and without coma and with or without focal neurological signs. None of the variables were significantly associated with these parameters (data not presented).

**Correlation between variables.** Our analysis focused on variables associated with death, and only data from the first 7 days of treatment were included. Figure 6 presents the rela-
Figure 4. Mean cerebrospinal fluid (CSF) concentrations (with 95% confidence intervals) of metalloproteinase (MMP)-9 and tissue inhibitors of MMPs (TIMPs) (the horizontal line represents the limit of detection of the assay) and log_{10} of the albumin and IgG indices over the treatment period (normal ranges indicated by horizontal lines) are shown. A, CSF MMP-9 levels. B, CSF TIMP-1 levels. C, Log_{10} values of the albumin index. D, Log_{10} values of the IgG index.

tionships among CSF lactate, CSF IL-8, and CSF IFN-γ. CSF lactate was correlated with CSF IL-8 (r = 0.727; P < .001), CSF TNF-α (r = 0.584; P < .001), CSF IFN-γ (r = 0.758; P < .001), and CSF TIMP-1 (r = 0.521; P = .002). The CSF IL-10 concentration was correlated with CSF WCC (r = 0.497; P = .001) and IgGI (r = 0.527; P = .001). The CSF:blood glucose ratio was weakly correlated with CSF IL-8 (r = 0.387; P = .004), CSF WCC (r = 0.284; P = .031), IgGI (r = 0.327; P = .026), and CSF lactate (r = −0.351; P = .039). MMP-9 levels were correlated with CSF IL-8 (r = 0.476; P = .001) and IFN-γ (r = 0.513; P = .001) and showed a weak association with TIMP-1 (r = 0.320; P = .041), CSF protein (r = 0.298;
Figure 5. The relationship is shown between cerebrospinal fluid (CSF) lactate, CSF interleukin (IL)-8, and CSF interferon (IFN)-γ levels during the first 7 days of treatment, giving the correlation coefficient ($r$) and $P$ by Spearman’s test of correlation. A, The relationship between CSF lactate and CSF IL-8. B, The relationship between CSF lactate and IFN-γ. C, The relationship between CSF IL-8 and IFN-γ.

$P = .034$), and CSF lactate ($r = 0.362; P = .042$). CSF concentrations of TIMP-1 were correlated with CSF lactate ($r = 0.502; P = .009$), CSF IL-8 ($r = 0.5; P = .001$), and IFN-γ ($r = 0.574; P = .001$). No significant relationship was found among MMP-9, TIMP-1, and the AI and IgG1 or among CSF neutrophil count, CSF IL-8 concentration, and the length of symptoms before treatment.

DISCUSSION

The present study monitored 21 HIV-negative adult patients throughout their treatment for TBM (none of the patients received corticosteroids). The concentrations of various pro- and anti-inflammatory indices were recorded on serial CSF samples, the timing of which reflected the clinically important periods of
the disease. The CSF specimen taken at the end of ATC (9 months) served as an important indicator of successful treatment and as a control for those samples taken earlier in the infection.

Ninety percent of deaths from TBM occur during the first month of treatment [16]. Deaths after this period are usually caused by complications arising from neurological sequelae, such as sepsis originating from the respiratory or urinary tract. A favorable prognosis is dependent on starting ATC before the onset of coma [17]. These facts suggest that the inflammatory response immediately before and after starting ATC is critical to the outcome of the patient. Previous studies have shown that CSF parameters respond slowly to treatment [18, 19], and the requirement for 6–12 months of chemotherapy suggests a prolonged inflammatory response.

In the present study, blood and CSF samples taken before the start of ATC revealed a highly compartmentalized immune response. Concentrations of CSF IL-8 were ~40 times that of blood, and neither IFN-γ nor TNF-α was detectable in blood, despite easily detectable concentrations in the CSF (figure 2). IL-8 is an inflammatory chemokine that is produced by many cell types and functions as a chemoattractant for neutrophils and a subset of T lymphocytes. When macrophages phagocytose M. tuberculosis in vitro, they express IL-8 in a TNF-α- and IL-1β-dependent manner [20]. IL-8 has been detected in plasma [21] and bronchoalveolar lavage fluid [22] from patients with pulmonary tuberculosis and, as we observed in the present study, remained detectable for many months. The mechanisms driving the prolonged expression of IL-8 in a disease that is not characterized by a strong neutrophilic response are unknown.

IFN-γ and TNF-α have been recognized as key cytokines in the control of M. tuberculosis infection [23]. T cells and NK cells produce IFN-γ in response to M. tuberculosis infection, but absolute levels may be an unreliable correlate of protection [24]. We found high concentrations of CSF IFN-γ before treatment, but there was no association with outcome. The results of animal studies have suggested that TNF-α is central to TBM pathogenesis, given that the inhibition of TNF-α improves outcome [4]. We found, as have previous reports, low pretreatment concentrations of CSF TNF-α, and there was no association between CSF TNF-α concentration and death. However, the biological activity of TNF-α may depend on the relative concentrations of its soluble receptors, which may antagonize the biological effects of TNF-α at high concentrations and promote them at low concentrations [25]. In our study, the mean pretreatment concentration ratios of soluble TNF-α:TNF-α and TNF-α:TNF-α2:TNF-α, were 2.8 and 7.7, respectively, compared with the values of 27.2 and 28 reported by Rydberg et al. [7]. This suggests larger biologically active fractions of TNF-α in our group of patients, although it was unclear whether the CSF samples in Rydberg’s study were taken before or after treatment. Our results suggest that treatment reduces the CSF concentrations of TNF-α rapidly, while slowly reducing the receptor concentrations. By day 2 of treatment, the ratios of receptors to TNF-α increased to 9.9 and 18.1. This may have the paradoxical effect of prolonging the biological activity of TNF-α despite decreasing CSF concentrations. Further investigation is required to address this hypothesis.

In bacterial meningitis, it is hypothesized that bacterial lysis, which is induced by treatment with antibiotics, may contribute to the inflammation in the subarachnoid space and lead to a worse outcome [26]. The same may be true for TBM, which has been the rationale behind the administration of adjuvant corticosteroids for many years [27]. Our results provide little support for this hypothesis. Only the mean CSF WCC rose during the first 7 days of treatment (figure 1A), and, in all patients, regardless of outcome, ATC produced a rapid reduction in the CSF concentrations of IL-8, TNF-α, and IFN-γ (figure 2). This response is in contrast to the kinetics of the CSF WCC, CSF protein, CSF:blood glucose ratio, CSF IL-10, CSF TNF-α receptors (figure 3), and CSF MMP-9 and TIMP-1 (figure 4), all of which were either detectable or above the normal range after 60 days of chemotherapy. Evidence for the longevity of the immune response is supported by the extent and duration of the BBB breakdown (figure 6). These data suggest that there may be 2 phases of the inflammatory response in TBM. The first is characterized by high CSF concentrations of IL-8 and IFN-γ and lower concentrations of TNF-α that are rapidly attenuated by ATC. The severity of this phase can be assessed by the concentration of CSF lactate. The second phase is characterized by a persistent inflammatory response and a breakdown in the BBB, despite treatment, and may be maintained by the continued activity of CSF soluble TNF-α receptors and the relative concentrations of MMP-9 and TIMP-1.

The present study had limited power to associate the concentrations of any of these variables with death. However, the CSF lactate concentration appears to represent a good guide for prognosis: concentrations before and during the first 7 days of treatment were significantly higher in those who died (95% CI, 1.4–5.3; \( P = .001 \)). Lactate is produced in all tissues in response to hypoxia. TBM causes an obliterative vasculitis with ischemia, and often infarction [28], and the CSF lactate concentration may reflect the severity of this process. CSF IL-8, IFN-γ, TNF-α, MMP-9, and TIMP-1 levels were all significantly correlated with CSF lactate, which suggests that these molecules might be associated with pathogenesis. The CSF cellular response also appeared to be significant for outcome: death was associated with a lower CSF WCC by univariate (95% CI, −68 to −584; \( P = .014 \)) and multivariate (OR, 0.98, 95% CI, 0.97–0.99; \( P = .027 \)) analyses. This is a surprising finding: previous reports have associated low CSF WCC with older age [29] and
HIV infection [17], which suggests an attenuated CSF cellular response as part of a systemic immune paresis. The phenotype of the cellular response may also carry prognostic significance. Survival was associated with a lower percentage of lymphocytes and a higher percentage of neutrophils (table 1). Murine studies have suggested that neutrophils may have a protective role against *M. tuberculosis* infection [30]. The correlation between total CSF WCC and the CSF IL-10 concentration may also be significant. It is tempting to speculate that IL-10 derived from infiltrating white blood cells might mediate immunosuppressive activity in the subarachnoid space. Before these hypotheses can be addressed, the functional phenotype of the CSF white cells needs to be characterized. There is evidence that γδ T cells may be important in the CSF response to *M. tuberculosis* [31], but serial flow-cytometric analysis of CSF is required to further define the cellular immune response. Larger studies are required to further characterize the molecules and cells that are important for pathogenesis and outcome. These may suggest alternative therapeutic approaches that might supersede the blind use of corticosteroids.

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**References**