Differential Elevation of Circulating Interleukin-1β, Tumor Necrosis Factor Alpha, and Interleukin-6 in AIDS-Associated Cachectic States

LAURENT BÉLEC,1,4 DOMINIQUE MEILLET,2 ALAIN HERNVANN,3 GERARD GRÉSENGUET,7 AND ROMAIN GHERARDI5

Service de Microbiologie (Virologie), Hôpital Broussais,1 Service de Biochimie, Hôpital de la Salpêtrière,2 and Service de Biochimie, Hôpital Laennec,3 Paris, and Département de Pathologie (Neuropathologie), Hôpital Henri Mondor, Créteil,5 France, and Centre National Hospitalier Universitaire de Bangui and Institut Pasteur de Bangui, Bangui, Central African Republic4

Received 5 April 1993/Returned for modification 27 May 1993/Accepted 8 July 1993

Elevation of serum interleukin-1β (IL-1β) levels, and to a lesser degree tumor necrosis factor alpha levels, was found in cachectic human immunodeficiency virus (HIV)-infected African patients without concurrent opportunistic infection or neoplasia (HIV wasting syndrome). A heterogeneous pattern of elevations of cytokine levels, including mild elevations of IL-1β and pronounced elevations of IL-6 levels, was found in other cachectic states.

Cachexia is frequently observed in patients with AIDS, especially in Africa south of the Sahara, where 60 to 80% of patients present with the so-called “slim disease” (11). In nearly half of the cases, it corresponds to the human immunodeficiency virus wasting syndrome (HIV-WS) (1), in which no cause of cachexia other than HIV itself can be demonstrated.

African Republic. All had weight loss (>20%), with muscle weakness and with prolonged fever or chronic diarrhea (11). They were evaluated by diagnostic procedures available in Africa south of the Sahara and classified as having cachexia without (group I) or with (group II) concurrent opportunistic infection or neoplasia. Patients in group I had HIV-WS

<table>
<thead>
<tr>
<th>Patient type (n)</th>
<th>Mean level (pg/ml) in serum of:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IL-1β</td>
</tr>
<tr>
<td>HIV negative (7)</td>
<td>8.8 ± 10.1 (0-25)</td>
</tr>
<tr>
<td>HIV positive, asymptomatic control (7)</td>
<td>8.8 ± 7.4 (0-20)</td>
</tr>
<tr>
<td>HIV positive with cachexia (33)</td>
<td>246 ± 306 (10-1,390)</td>
</tr>
<tr>
<td>Group I (15)6</td>
<td>403 ± 391 (20-1,390)</td>
</tr>
<tr>
<td>Group II (18)7</td>
<td>114 ± 100 (10-300)</td>
</tr>
</tbody>
</table>

a Values are means ± standard deviations; ranges are in parentheses.

b HIV-positive patients with HIV-WS.

c HIV-positive patients with other AIDS cachexias.

Among the variety of possible causes of AIDS cachexia (6), one attractive hypothesis involves cytokines that are overproduced by monocytes/macrophages (3, 6, 8–10, 14) and can induce cachexia in animal models. They include interleukin-1 (IL-1) (7), tumor necrosis factor alpha (TNF-α) (17), and IL-6 (16), which together form the monokine network (15).

To evaluate the possible role of cytokines in cachectic states associated with AIDS, we evaluated concentrations of IL-1β, TNF-α, and IL-6 in the sera of African patients.

Patients. Thirty-three HIV type 1 (HIV-1)-infected patients (18 women and 15 men; age [mean ± standard deviation], 28 ± 6 years) were included prospectively in Bangui, Central Africa south of the Sahara.

According to Centers for Disease Control criteria (18).

Methods. Levels of cytokines in serum were measured in duplicate by enzyme-linked immunosorbent assay (Immuno-tech, Marseille, France [IL-1β]; Medgenix, Fleurus, Belgium [TNF-α and IL-6]). As increased circulating levels of IL-1 inhibitors could mask the biological activity of IL-1 overproduction (2), we measured C-reactive protein by immunonephelometry (Behring, Marburg, Germany) as an indicator of the biological activities of IL-1β and IL-6 (4). Seven healthy HIV-1-seronegative African men (mean age, 24.8 ± 3.2 years) were used to determine the normal value (mean ± 2 standard deviations). Seven asymptomatic HIV-1-infected African men with normal weight (mean age, 27.3 ± 5.1 years) were used as controls. Student’s t test, the x² test, and Spearman’s test were used for statistical analyses.

Clinical groups. All 33 patients had diffuse amyotrophy,
Serum interleukin-18

Serum interleukin-6

Serum tumor necrosis factor-alpha

Serum C-reactive protein

FIG. 1.

FIG. 2.
anorexia, and extreme fatigue; 20 had fever; and 17 had diarrhea. Fifteen (45%) had HIV-WS (group I). Among the other patients (group II), 6 had pulmonary tuberculosis, 3 had Kaposi's sarcoma, 2 had lymph node tuberculosis, 4 had digestive tract infections (Isospora hominis, Salmonella speciea, and Candida albicans), 1 had cryptococcal meningoencephalitis, and 2 had focal symptoms suggestive of cerebral opportunistic infection or neoplasia.

**IL-1β, TNF-α, and IL-6 levels (Fig. 1 and 2; Table 1).** Levels of monokines were elevated in the sera of 28 of 33 cachectic patients. Levels of the three cytokines were elevated in 10 patients, those of both IL-1β and TNF-α were elevated in 3 patients, those of both IL-1β and IL-6 were elevated in 6 patients, and those of a single cytokine were elevated in 9 patients (IL-1β, 3 patients; TNF-α, 1 patient; and IL-6, 5 patients).

Levels of IL-1β were elevated in 22 (67%) cachectic patients and in none of the 7 HIV-positive control patients (P < 0.001). Levels of IL-1β were elevated in 13 of 15 patients with HIV-WS (P < 0.001). In patients with opportunistic infection or neoplasia, levels of IL-1β were increased (P < 0.02) less frequently than in group I patients (9 of 18 patients; P < 0.05) and to a lesser degree (P < 0.01).

TNF-α levels were high in 14 cachectic patients, including 8 patients with HIV-WS, and showed large interindividual variations. The prevalence of TNF-α increase in cachectic patients did not differ from that in HIV-positive control patients. In contrast, the levels of TNF-α in serum were higher in group I patients than in control patients (P < 0.05).

Prevalences of IL-6 increase in cachectic patients (21 of 33 patients) and group I patients (7 of 15 patients) did not differ from those in HIV-positive controls. In group II patients, both the frequency (14 of 18 patients; 78%) and the degree of the elevation of IL-6 levels were significantly higher than those in control patients (P < 0.05). The IL-6 levels were more frequently elevated in group II than in group I patients (P < 0.05).

In cachectic patients and in group I patients, there were positive correlations between the levels of TNF-α and IL-6 (groups I and II, P < 0.01; group I, P < 0.02) and between the levels of IL-1β and IL-6 (groups I and II, P = 0.001; group I, P < 0.03). High TNF-α levels were more frequently found in patients with diarrhea than in the other patients (11 of 17 versus 3 of 16; P < 0.01). Patients with Kaposi's sarcoma had increased IL-6 levels. The levels of C-reactive protein in serum (24 ± 27 mg/liter) were elevated in 16 of 33 patients (group I, 26%; group II, 67%), who usually (11 of 16) also had elevation of both IL-1β and IL-6 levels in their serum. In group II patients, C-reactive protein levels correlated positively with those of IL-6 (P < 0.05).

Finally, group I patients had striking elevations of the levels of IL-1β, and to a lesser degree of TNF-α, while group II patients showed a heterogeneous pattern of cytokine level elevation in serum that included a mild increase of IL-1β and a pronounced increase of IL-6 in most patients.

The overlapping effects of IL-1β and TNF-α include induction of anorexia; loss of body weight; lipid, and cell mass; fat weight loss (5, 7, 12, 17). Monokines are endogenous pyrogens (4, 5); TNF-α induces diarrhea in experimental models (13); IL-1β induces slow-wave sleep and likely mediates sickness behavior (5). These findings suggest that monokines in our patients may have contributed to the genesis of their clinical symptoms.

Reddy and Grieco found detectable IL-1β in serum of 34% of patients with AIDS (14). In our study, IL-1β was detected in 100% of patients with HIV-WS, and its level was elevated in 87% of them. Mean levels of IL-1β and TNF-α, but not of IL-6, were higher in patients of this group than in those of group II. The pulsatile release of cytokines may have precluded detection of abnormal monokine production in some cases. In patients with pre-AIDS or AIDS, Lepe-Zuniga et al. identified a subset of subjects (58%) who spontaneously produced high amounts of IL-1 (9). It is conceivable that HIV-WS occurs in a subgroup of patients with the particular ability to produce high monokine levels.

In cachectic patients of group II, a cocktail of monokines was found in serum, with less IL-1β and more IL-6 than in patients of group I. This was in keeping with the role of IL-6 in the acute response to infections (4) and its suppressive effect on IL-1β and TNF-α production (15).

We conclude that the synergistic action of monokines may contribute to cachectic states and related symptoms in patients with AIDS and that HIV-WS is mainly associated with IL-1β and TNF-α overproduction.

**REFERENCES**


