Natural History of Human T-Lymphotropic Virus 1–Associated Myelopathy

A 14-Year Follow-up Study

Stéphane Olindo, MD; Philippe Cabre, MD; Agnes Lézin, PhD; Harold Merle, MD; Martine Saint-Vil, MD; Aissatou Signate, MD; Michael Bonnan, MD; Aurélie Chalon, PhD; Lionel Magnani, MD; Raymond Césaire, MD, PhD; Didier Smadja, MD

Background: The progression of neurological disability in human T-lymphotropic virus 1 (HTLV-1)–associated myelopathy/tropical spastic paraparesis (HAM/TSP) remains undefined.

Objectives: To determine the time course of disability scores and to identify predictors of outcome among patients with HAM/TSP.

Design: Clinical 14-year follow-up study.

Setting: University hospital.

Patients: One hundred twenty-three patients with HAM/TSP.

Main Outcome Measures: We determined time from onset to the following 4 Kurtzke Disability Status Scale (DSS) end points: scores of 6 (unilateral aid required), 6.5 (bilateral aid required), 8 (wheelchair confinement), and 10 (death related to the disease). Times to reach selected DSS scores were estimated using the Kaplan-Meier method. Univariate and multivariate analyses identified variables related to the rate of progression to DSS 8. The HTLV-1 proviral loads were also assessed.

Results: The disability of the cohort progressed throughout the follow-up period. The median times from onset to DSS 6, 6.5, and 8 were 6, 13, and 21 years, respectively. The median time from DSS 6 to DSS 8 was 8 years; DSS 10 was reached by one fourth of the patients within 20 years. Age at onset of 50 years or older and high HTLV-1 proviral load were associated with a shorter time to DSS 8 (P = .01 and P = .02, respectively). A shorter time to DSS 6 significantly adversely affected the time to progression from DSS 6 to DSS 8.

Conclusions: Human T-lymphotropic virus 1–associated myelopathy/tropical spastic paraparesis is a rapidly disabling disease. Monitoring for HTLV-1 proviral load is recommended in future therapeutic trials.

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clinical follow-up study between January 1, 1990, and December 31, 2004, among a cohort of 123 patients.

**METHODS**

**PATIENT POPULATION AND DATA COLLECTION**

The population in Martinique (French West Indies) at the 1999 census was 381,427, the life expectancy was 75.2 years for men and 81.7 years for women, and 2.2% of the population was se-ropositive for HTLV-1 in 1989.25 Patients with HAM/TSP followed up in the Department of Neurology, University Hospital of Fort de France constituted the entire cohort. All patients were Afro-Caribbean. Our department is the only neurological facility for patients in Martinique and accepts referrals directly from practitioners and other hospitals and receives a wide cross section of patients. The association of TSP with HTLV-1 was first demonstrated in 1985 in a serological study conducted in our department. Only symptomatic treatments are usually given to patients with HAM/TSP, because no effective specific treatment has been reported, to our knowledge.

An archive of research medical records from patients with HAM/TSP was begun in 1991, which was kept separate from the hospital records. The research medical record collection includes all patients with a diagnosis of HAM/TSP who were examined at least once at the Department of Neurology. Since 1996, data were recorded using StatView software version 5.0 (SAS Institute, Cary, NC). Data were entered retrospectively when the patient was first seen in the Department of Neurology and at each follow-up visit. In the absence of reliable information about the year of onset of a disability step, the database cell was left blank.

The clinical variables examined were sex, age, age at onset, initial symptom (gait impairment or urinary disturbances), and history of blood transfusion before 1989 (the first year of blood bank screening for HTLV-1 in Martinique). A complete ophthalmologic examination was conducted to detect uveitis and dry keratoconjunctivitis.

Biopsy specimens of minor salivary glands were obtained, with results expressed according to Chisholm grade.24 Bronchialveolar lavage was performed under local anesthesia. T lymphocytes were identified and counted, and alveolitis was confirmed when lymphocytes represented more than 15% of the total alveolar cells. Cerebrospinal fluid immunoelectrophoresis was conducted to detect M protein and oligoclonal bands. Since 1995, peripheral blood mononuclear cells (PBMCs) were isolated from EDTA-enhanced blood by density gradient centrifugation and were cryopreserved until use, and since 2000, HTLV-1 proviral load (PL) has been quantified. DNA was extracted from $10^6$ cells using a phenol-chloroform procedure. The HTLV-1 PL was quantified using a real-time TaqMan polymerase chain reaction method (Applied Biosystems, Norwalk, Conn.) and was expressed as the number of HTLV-1 copies per $10^6$ PBMCs.

**DEFINITION OF CASES**

As of December 31, 2004, 132 patients had been included in the database. The diagnosis of HAM/TSP was made according to World Health Organization criteria.27 Briefly, the illness is diagnosed in the presence of the following: (1) a slowly progressive paraparesis with urinary disturbances caused by a symmetrical myelopathy involving predominantly the pyramidal tracts, (2) antibodies to HTLV-1 in serum, and (3) antibodies to HTLV-1 in cerebrospinal fluid. Since 1998, magnetic resonance imaging has replaced myelography to rule out spinal cord compression. Patients had no brain, brainstem, or cerebellar disturbances or any history of optic neuropathy suggestive of multiple sclerosis.

**ASSESSMENT OF PATIENTS**

Patients were seen on a yearly basis. However, in the absence of specific effective treatment, this was not the case for all patients, especially among those becoming severely disabled. Extensive efforts were made to track down patients. We attempted to contact directly the patients, their family physician, their rehabilitation physician, their relatives, or their neighbors. The cause of death was identified through hospital records or family physician medical records. Necessarily, a few arbitrary decisions were made regarding the cause of death in cases in which the clinical records were suboptimal. Bedridden patients who developed sepsis, pneumonia, nephritis, or pulmonary embolism were considered to have died of HAM/TSP. On the other hand, if the cause of death was listed as cancer, heart disease, or some other disorder unrelated to HAM/TSP, such patients were considered not to have died of HAM/TSP.

The year of first symptoms, such as stiffness or weakness in the legs or urinary disturbances, defined the year of HAM/TSP onset. Neurological disability was assessed at each visit to the Department of Neurology using the Kurtzke Disability Status Scale (DSS). We focused on scores that could be easily determined retrospectively, namely, scores of 6 (ability to walk with unilateral support ≤100 m without rest), 6.5 (need of bilateral aid to walk 20 m), 8 (essential restriction to a wheelchair), and 10 (death related to the disease). We did not consider the lower DSS score (<6) in our analysis because the first clinical symptoms in HAM/TSP usually include gait impairment. Years of assignment of scores of 6, 6.5, and 8 were unavailable in 6, 11, and 0 cases, respectively.

By examining survival to DSS 8, we examined the effect of the following variables on the time to reach severe motor disability in HAM/TSP: sex, age at onset (<50 vs ≥50 years), early disability, presence of ophthalmologic abnormalities, high Chisholm score of 3 to 4, high bronchoalveolar alveolitis rate (≥30%), presence of intrathecal IgG synthesis (IgG index ≥0.7 and presence of oligoclonal bands), and high HTLV-1 PL (>10⁵/10⁶ PBMCs). The rate of early disability was examined by dividing the patients into 2 groups depending on the time of progression to DSS 6. We arbitrarily used a cutoff time of 3 years and compared the groups who reached DSS 6 during and after this period.

**STATISTICAL ANALYSIS**

Survival was estimated according to the Kaplan-Meier method. The end point was the time to irreversible disability, as indicated by scores of 6, 6.5, 8, and 10 on the Kurtzke DSS. The log rank test was used for univariate analyses to identify variables related to the rate of progression from onset to DSS 8. Factors of potential significance in univariate analyses (defined as $P<.25$) were then introduced in a multivariate Cox proportional hazards regression model in a stepwise fashion. The level of statistical significance was set at $P<.05$. All computations were performed using StatView version 5.0 software.

**RESULTS**

**CHARACTERISTICS OF THE PATIENTS**

Of 132 patients who were potentially eligible for the study, 5 (3.8%) were unavailable for follow-up, and 4 (3.0%) were excluded because of lack of confidence in the diagnosis (2 had structural cervical myelopathy, 1 had symp-
tomatic lumbar stenosis, and 1 had hysterical symptoms). The baseline characteristics of the remaining 123 patients with HAM/TSP are given in Table 1.

LABORATORY STUDIES

The laboratory data collected at the time of diagnosis in patients having HAM/TSP are summarized in Table 2. The HTLV-1 PLs in PBMCs are also given.

HAM/TSP DISABILITY COURSE

Time From HAM/TSP Onset to DSS 6, 6.5, and 8

Among 123 patients, 100 (81.3%), 70 (56.9%), and 45 (36.6%) reached the end point scores of 6, 6.5, and 8, respectively, on the DSS during follow-up. The median times from onset of HAM/TSP to the assignment of DSS scores of 6, 6.5, and 8 were 6 years (95% confidence interval [CI], 5-7 years), 13 years (95% CI, 10-17 years), and 21 years (95% CI, 14-28 years), respectively (Figure 1).

Time From HAM/TSP Onset to Death Related to the Disease

Among 123 patients, 22 (17.8%) died, 19 (15.4%) of HAM/TSP and 3 (2.4%) of other causes. One fourth of the patients reached DSS 10 within 20 years (95% CI, 14-27 years) (Figure 1). The mean±SD age at the time of death due to HAM/TSP was 63.0±16.7 years and due to other causes was 69.0±8.8 years (P = .57). The causes of death are listed in Table 3.

INITIAL VARIABLES AND TIME FROM ONSET TO DSS 8

We analyzed several initial clinical and biological variables to assess their usefulness in predicting the long-term prognosis of patients with HAM/TSP. These are summarized in Table 4.
set (24 vs 14 years, P = .02) (Figure 2). Sex, history of blood transfusion, and initial symptom of HAM/TSP (gait impairment vs urinary disturbances) did not affect the disease course. The median time to DSS 8 was notably shorter among patients who visited our department within the first 3 years of the disease compared with those who have visited us more than 3 years after onset of the disease.

Although most of the intervals from onset to wheelchair confinement were shorter in patients with systemic manifestations, the differences did not reach statistical significance. The presence of intrathecal IgG synthesis did not affect the HAM/TSP rate of progression, whereas a high HTLV-1 PL (>10^5/10^6 PBMCs) was strongly associated (P = .007) with a shorter median time from onset to the assignment of a DSS score of 8 than patients with a low HTLV-1 PL (Figure 3).

### INITIAL VARIABLES AND TIME TO PROGRESSION FROM DSS 6 TO DSS 8

The median time from the assignment of a DSS score of 6 to the assignment of a score of 8 was 8 years (95% CI, 6–12 years). This was unaffected by other variables analyzed in this study. Time from onset to DSS 6 was the only variable that affected the time of progression from DSS 6 to DSS 8. Figure 4 shows a significant difference in the median time from disease onset to assignment of a score of 8 on the Kurtzke Disability Status Scale (DSS) according to a younger vs an older age at onset.

### Table 4. Univariate Analysis of Kaplan-Meier Estimates of the Time From Disease Onset to Kurtzke Disability Status Scale (DSS) 8 According to Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients, No. (%)</th>
<th>Median Time (95% Confidence Interval), y</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>27 (22.0)</td>
<td>17 (11-28)</td>
<td>.4</td>
</tr>
<tr>
<td>Female</td>
<td>96 (78.0)</td>
<td>22 (15-28)</td>
<td></td>
</tr>
<tr>
<td><strong>Age at onset, y</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>68 (55.3)</td>
<td>24 (21-28)</td>
<td>.02</td>
</tr>
<tr>
<td>≥50</td>
<td>55 (44.7)</td>
<td>14 (13-NA)</td>
<td></td>
</tr>
<tr>
<td><strong>Blood transfusion before 1989</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>25 (26.6)</td>
<td>28 (22-28)</td>
<td>.2</td>
</tr>
<tr>
<td>No</td>
<td>69 (73.4)</td>
<td>21 (16-27)</td>
<td></td>
</tr>
<tr>
<td><strong>Initial symptom</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gait impairment</td>
<td>86 (86.0)</td>
<td>21 (17-26)</td>
<td>.8</td>
</tr>
<tr>
<td>Urinary disturbances</td>
<td>14 (14.0)</td>
<td>21 (14-NA)</td>
<td></td>
</tr>
<tr>
<td><strong>Initial clinic visit within 3 y</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>63 (51.2)</td>
<td>14 (9-18)</td>
<td>.01</td>
</tr>
<tr>
<td>No</td>
<td>60 (48.8)</td>
<td>24 (19-28)</td>
<td></td>
</tr>
<tr>
<td><strong>Assignment of DSS 6 within 3 y</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>37 (38.5)</td>
<td>7 (4-12)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No</td>
<td>59 (61.5)</td>
<td>28 (15-28)</td>
<td></td>
</tr>
<tr>
<td><strong>Uveitis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>15 (17.6)</td>
<td>14 (7-NA)</td>
<td>.2</td>
</tr>
<tr>
<td>No</td>
<td>70 (82.4)</td>
<td>28 (14-28)</td>
<td></td>
</tr>
<tr>
<td><strong>Keratitis</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>13 (15.9)</td>
<td>21 (14-28)</td>
<td>.48</td>
</tr>
<tr>
<td>No</td>
<td>69 (84.1)</td>
<td>NA</td>
<td></td>
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<tr>
<td><strong>Dry keratoconjunctivitis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>36 (43.9)</td>
<td>14 (14-NA)</td>
<td>.27</td>
</tr>
<tr>
<td>No</td>
<td>46 (56.1)</td>
<td>28 (17-28)</td>
<td></td>
</tr>
<tr>
<td><strong>Chisholm score of 3-4</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>38 (48.1)</td>
<td>24 (9-28)</td>
<td>.15</td>
</tr>
<tr>
<td>No</td>
<td>41 (51.9)</td>
<td>NA (14-NA)</td>
<td></td>
</tr>
<tr>
<td><strong>Alveolitis &gt;30%</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>30 (52.6)</td>
<td>21 (14-NA)</td>
<td>.15</td>
</tr>
<tr>
<td>No</td>
<td>27 (47.4)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td><strong>IgG index &gt;0.7</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>39 (48.1)</td>
<td>21 (14-NA)</td>
<td>.4</td>
</tr>
<tr>
<td>No</td>
<td>42 (51.9)</td>
<td>24 (17-28)</td>
<td></td>
</tr>
<tr>
<td><strong>Intrathecal oligoclonal bands</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>47 (58.8)</td>
<td>24 (14-28)</td>
<td>.4</td>
</tr>
<tr>
<td>No</td>
<td>33 (41.3)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td><strong>HTLV-1 proviral load &gt;10^5/10^6 PBMCs</strong></td>
<td></td>
<td></td>
<td>.007</td>
</tr>
<tr>
<td>Yes</td>
<td>46 (45.5)</td>
<td>14 (12-28)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>55 (54.5)</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: HTLV-1, human T-lymphotropic virus 1; NA, not available; PBMCs, peripheral blood mononuclear cells.
The rapidity of HAM/TSP progression is apparent, with half of the patients reaching DSS 6, 6.5, and 8 by 6, 13, and 21 years, respectively. The median time to progression from a score of DSS 6 to wheelchair confinement was 8 years. To our knowledge, there are no data in the literature concerning the time to reach disability end points in HAM/TSP.

The progression of HAM/TSP has mainly been analyzed in cross-sectional studies. The disease course is usually described as varying widely among patients, and several investigators have shown that a subgroup of patients experiences rapid disease progression. We confirmed that a subgroup of patients has a faster rate of progression. While the median time from onset to wheelchair confinement was 7 years among patients who reached DSS 6 within 3 years, the median time was 28 years among those reaching DSS 6 after this period. Earlier studies speculated that disability progression occurs in the initial stage of the illness, reportedly during the first year in a study by Araujo et al., and becomes stable after this step. The results of our study disagree with this progression spectrum of HAM/TSP and show that motor disability progresses throughout the entire follow-up period. Our longitudinal data and the previous transversal findings are difficult to compare, and disagreement may result from methodological differences. In a study with 4 years of follow-up, only 17% of patients with HAM/TSP experienced significant disability progression, whereas in another study one half of 64 patients with HAM/TSP followed-up for 10 years showed significant disability deterioration. The results of these 2 studies suggest that a long follow-up period is required to reveal meaningful changes in disability. What seems to emerge from the data as a whole is that motor disability worsens throughout the entire disease course.

The disability progression seems slightly more favorable in primary progressive multiple sclerosis than in HAM/TSP. However, the natural history data from population-based cohorts with primary progressive multiple sclerosis demonstrate results similar to our findings in patients with HAM/TSP, with the assignment of DSS 6 from onset of primary progressive multiple sclerosis ranging from 6 to 8 years and a median time from onset to DSS 8 of 18 years in a London, Ontario, cohort.

MORTALITY DATA

Among patients who died during the study, a high proportion (86.4% [19/22]) died as a direct result of the complications of HAM/TSP. The mean age at death from HAM/TSP was about 15 years younger than the life expectancy in Martinique (63 years vs 75.2 years for men and 81.7 years for women).

COMMENT

Natural history data are of clear importance in designing clinical trials and in assessing the effect of treatment. This observational study of the natural history of HAM/TSP provides new data on the progression of neurological disability. The demographic characteristics of our HAM/TSP cohort are in accord with previous studies, particularly the preponderance of women (78%) and the age at onset around 50 years. In this analysis, the median time for patients to be first seen in the Department of Neurology was 3 years, and by this time only 30% and 9% of patients had reached DSS 6 and DSS 8, respectively (data not shown). Therefore, most data were obtained from prospective observations.

CLINICAL COURSE

The disability progression seems slightly more favorable in primary progressive multiple sclerosis than in HAM/TSP. However, the natural history data from population-based cohorts with primary progressive multiple sclerosis demonstrate results similar to our findings in patients with HAM/TSP, with the assignment of DSS 6 from onset of primary progressive multiple sclerosis ranging from 6 to 8 years and a median time from onset to DSS 8 of 18 years in a London, Ontario, cohort.

MORTALITY DATA

Among patients who died during the study, a high proportion (86.4% [19/22]) died as a direct result of the complications of HAM/TSP. The mean age at death from HAM/TSP was about 15 years younger than the life expectancy in Martinique (63 years vs 75.2 years for men and 81.7 years for women).
The follow-up was too short to determine the median time from disease onset to DSS 10. One fourth of the patients died of complications related to HAM/TSP within 20 years of onset.

PROGNOSTIC INDICATORS

We identified 3 subpopulations among patients with HAM/TSP who have a notably poor prognosis. The first group consists of patients who have a high HTLV-1 PL (>10⁷/10⁶ PBMCs) (P = .007). This finding is consistent with a recent cross-sectional study showing that a high HTLV-1 PL was associated with a rapid disease course. The HTLV-1 PL was not quantified in the early phases of the disease in all patients. However, HTLV-1 PL seems stable during the course of the illness and is not correlated with disease duration. The second group consists of patients with an age at onset of 50 years or older, who experience a more disabling course of HAM/TSP (P = .02). Immunosuppression is a factor associated with HAM/TSP development. Older age constitutes an immunosuppressed condition, which could explain the relationship between older age at onset and disease severity. The third group with a poor prognosis consists of patients with an early rate of progression. Among patients reaching DSS 6 within 3 years and after 3 years, the median times to progression from DSS 6 to DSS 8 are 4 years and 11 years, respectively (P = .007).

Wheelchair confinement occurred sooner in patients evaluated in the Department of Neurology within the first 3 years of disease onset than in those who were evaluated after this period. The median time to wheelchair confinement was 14 vs 24 years (P = .01).

In the present study, sex was unrelated to the rate of progression, whereas in a recent transversal study comparing 2 groups of 22 patients each with HAM/TSP, the authors found a worse prognosis among women. In our study, history of blood transfusion and initial symptom (gait impairment vs urinary disturbances) had no discernible effect on the rate of progression to DSS 8. In agreement with recent findings, the presence of IgG synthesis in cerebrospinal fluid did not affect disability progression. Although the median intervals from disease onset to DSS 8 were longer in patients with systemic manifestations than in those without, the differences between the 2 groups did not reach statistical significance.

The multivariate model of older age at disease onset and high HTLV-1 PL predicts a high rate of progression from onset to DSS 8. This model, which strengthens the results of the univariate analysis, is useful to predict disease severity, as these 2 variables are readily available at the time of HAM/TSP diagnosis.

In areas where HTLV-1 is endemic, HAM/TSP is a rapid disabling disease that may constitute a socioeconomic challenge. Older age at onset and high HTLV-1 PL are 2 independent factors associated with a poor prognosis. High disability levels among patients with HAM/TSP may be affected by therapeutic approaches aimed at reduction of HTLV-1 PL in PBMCs. Such treatment could be more effective in the early phases of the disease, particularly before the assignment of a DSS score of 6. The HTLV-1 PL in PBMCs seems to have a prognostic role in HAM/TSP, and the inclusion of this variable as a secondary end point in clinical trials is recommended.

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Correspondence: Stéphane Olindo, MD, Department of Neurology, University Hospital of Fort de France, Fort de France, 97200 Martinique (stéphane.olindo@chu-fortdefrance.fr).

Author Contributions: Study concept and design: Olindo, Cabre, Cesaire, and Smadja. Acquisition of data: Olindo, Cabre, Lézin, Merle, Saint-Vil, Signate, Bonnan, and Chalon. Analysis and interpretation of data: Olindo and Magnani. Drafting of the manuscript: Olindo. Critical revision of the manuscript for important intellectual content: Cabre, Lézin, Merle, Saint-Vil, Signate, Bonnan, Chalon, Magnani, Cesaire, and Smadja. Statistical analysis: Olindo, Lézin, and Magnani. Obtained funding: Cesaire. Administrative, technical, and material support: Olindo, Cabre, Merle, Saint-Vil, Signate, Bonnan, Chalon, Cesaire, and Smadja.

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