Disturbances in the Cerebral Perfusion of Human Immune Deficiency Virus-1 Seropositive Asymptomatic Subjects: A Quantitative Tomography Study of 18 Cases

Yves R. Tran Dinh, Hubert Mamo, Janine Cervoni, Charles Caulin, and Adrien C. Saimot

Quantitative measurements of cerebral blood flow (CBF) by xenon-133 ($^{133}$Xe) tomography, together with magnetic resonance imaging (MRI), electroencephalography (EEG), psychometric tests, and laboratory analyses were performed on 18 human immunodeficiency virus 1 (HIV-1) seropositive asymptomatic subjects. Abnormalities of cerebral perfusion were observed in 16 cases (88%). These abnormalities were particularly frequent in the frontal regions (77% of cases). MRI demonstrated leucoencephalopathy in only two cases. EEG showed only induced diffuse abnormalities in two cases. Psychometric tests showed restricted moderate disturbances in 55% of patients. These disturbances mostly concerned those sectors involved in cognitive functions and memorization. These results indicate that quantitative measurements of CBF by $^{133}$Xe-SPECT is capable of detecting abnormalities of cerebral perfusion at a very early stage (Phase II) of HIV-1 infection. These abnormalities are indications of disturbances resulting from unidentified metabolic or vascular lesions. This technique appears to be superior to MRI at this stage of the disease’s development. It could provide objective information leading to earlier treatment, and prove useful in evaluating potential antiviral chemotherapy.

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The pathogenic activity of the human immunodeficiency virus (HIV) is not restricted to T4 lymphocytes (1). The virus has other target cell populations, which also serve the CD4 membrane receptor proteins to which the virus binds before entering the cell (2). Several studies indicate that the brain is, with the immune system, a primary target for the virus (3–8). At the acquired immunodeficiency syndrome (AIDS) stage, in the absence of any opportunistic infection, the virus almost invariably attacks the brain, resulting in dementia or subacute encephalopathy (3,5,7,9). Tomographic imaging techniques, such as single-photon emission computed tomography (SPECT) cerebral blood flow (CBF) studies (10–12), positron emission tomography (PET) studies of cerebral metabolism (3,13–16) and magnetic resonance imaging (MRI) morphologic studies (17–20) have defined the location of AIDS-linked disturbances and the resulting dementia during the later stages of disease development.

However, the virus may invade the central nervous system (CNS) very early (6). The asymptomatic phase which follows seroconversion, Atlanta classification Phase II (21), is not synonymous with HIV viral quiescence, nor with the absence of developing cerebral lesions, as cognitive disturbances have been described at this stage (22). It is therefore most important to demonstrate the cerebral lesions, as their presence may well be very significant for the early initiation of chemotherapy. CT scans, neuropsychometric tests, and especially MRI, have all been proposed as possible means of early detection. Unfortunately, MRI and CT scans are both designed to detect morphologic changes, and these may not be apparent during the asymptomatic phase. While PET studies have been used in certain cases, this method is rather cumbersome for routine screening.

We therefore used Xenon-133 ($^{133}$Xe) SPECT to detect changes in CBF, as these changes are largely due to products of cerebral metabolism and vary with the energy needs of the brain (23,24). Our use of SPECT to determine any metabolic and/or circulatory anomalies in HIV-positive subjects is based on this coupling between CBF and neuronal metabolism. The diagnostic capacity of SPECT is compared with those of the other methods listed above, and we have demonstrated its...
use in detecting abnormalities of cerebral perfusion in Phase II HIV-1 seropositive subjects.

PATIENTS AND METHODS

Patients

Eighteen subjects, 2 women of Ghanaian or Angolan origin, and 16 homosexual or bisexual men aged from 25 to 68 yr (mean 32.6 ± 9.3 yr), were examined. All the patients had presented at the AIDS Detection Center at Hopital Lariboisière. The Center is open to all persons desiring free, anonymous serologic tests.

The subjects satisfied the following criteria:
1. All were HIV-seropositive after two successive ELISA tests, confirmed by Western blots. The virus was exclusively HIV-1, even in the two women of African origin. The exact dates of infection were not known.
2. None were drug-abusers. Drug-abusers were excluded from the study because of the potential risk of drug-induced alterations of cognitive functions and cerebral perfusion.
3. None showed neurologic focal signs or any opportunistic infections.
4. None had histories of cerebral infarct or any other vascular risk, diabetes, arterial hypertension, dyslipidemia, or hyperuricemia. Informed consent was obtained from all subjects.

Controls

Normal values were provided by nine volunteers, four men and five women medical students, mean age 22.2 ± 0.9 yr.

Methods

All subjects underwent a preliminary general clinical and neurologic examination. The following investigations were then performed:

1. Quantitative measurement of CBF by SPECT (Tomo-
matic 64, Medimatic, Copenhagen) using i.v. 133Xe (60 mCi). Measurements were made on patients at rest, with their eyes closed, in a quiet, darkened room to eliminate all external stimuli. The method has been described elsewhere (25,26). Three parallel slices located 1, 5, and 9 cm above the orbital-meatal plane, were obtained. Each slice was 2 cm thick and the spatial resolution was 1.7 cm. The selected regions of interest (Fig. 1) were automatically adapted to the size of each brain using a specific computer program (Head-independent region of interest software, Medimatic). The regional values were obtained for each selected region and compared to those of symmetric regions. Perfusion anomalies were determined by first analyzing the images visually, and then in terms of the regional values obtained by calculation. These values were compared to those obtained with the controls. All rCBF variations and inter-hemispheric asymmetries greater than the maximum 95% confidence interval of the control group (10%) were considered to be pathologic.
2. EEG, performed immediately after measuring CBF.
3. MRI, carried out within 15 days of CBF measurement.
4. Psychometric tests. A battery of neuropsychologic measurements was performed on all patients. These tests were designed to cover the major components of intellectual function, including memory, praxic ability, visual-motor coordination and concentration. The tests were: WAIS performance test, part of the WAIS verbal subset, the Wechsler memory scale, the Benton test, and Rey drawing.

RESULTS

Cerebral Blood Flow

CBF measurements of the asymptomatic HIV-1 seropositive subjects showed that the cerebral or cerebellar perfusion of 16 (88%) subjects was significantly less (≥10%) than that of the normal controls (Table 1). The extent of these brain anomalies varied; they affected a region or a hemisphere or were global. Two examples of the anomalies found by SPECT are shown in Figure 2. The unilateral or bilateral regions involved were: frontal region (14 cases, 77%); temporal region (10 cases, 55%); parietal region (8 cases, 44%); occipital region (11 cases, 61%); thalamic region (11 cases, 61%); and cerebellar region (11 cases, 61%) (Fig. 3).

There were diffuse reductions in CBF in two cases (Cases 11 and 17); four patients (Cases 1, 12, 15, 18) also showed crossed hemispheric and cerebellar hypoperfusion, suggesting the presence of a crossed cerebrocerebellar diachisis.

Other Tests (Table 2)

Laboratory Tests. The sedimentation rates were >10 mm in six cases (Cases 4, 5, 8, 11, 13, 17 with values of 24, 12, 48, 14, 20, and 72 mm, respectively, in the first hour). Many of the subjects had indication of

FIGURE 1

Preselected ROIs. The ROI are shown on the left side of each diagram: 1 = anterior temporal region; 2 = pons; 3 = cerebellar lobe; 4 = anterior frontal region; 5 = middle frontal region; 6 = sylvian area; 7 = temporo-parieto-occipital region; 8 = occipital region; 9 = thalamus area; 10 = superior frontal region; 11 = central region; and 12 = parietal region.
### Table 1

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Controls</th>
<th>Regions of Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Age</td>
<td>1L</td>
</tr>
<tr>
<td>F</td>
<td>22</td>
<td>47</td>
</tr>
<tr>
<td>M</td>
<td>23</td>
<td>46</td>
</tr>
<tr>
<td>F</td>
<td>24</td>
<td>40</td>
</tr>
<tr>
<td>M</td>
<td>22</td>
<td>40</td>
</tr>
<tr>
<td>F</td>
<td>23</td>
<td>50</td>
</tr>
<tr>
<td>M</td>
<td>21</td>
<td>39</td>
</tr>
<tr>
<td>F</td>
<td>22</td>
<td>40</td>
</tr>
<tr>
<td>M</td>
<td>23</td>
<td>50</td>
</tr>
</tbody>
</table>

**Mean**

| 22.2 | 51.8 | 56.2 | 53.0 | 52.0 | 61.7 | 61.7 | 51.6 | 51.0 | 55.9 | 55.8 | 48.2 | 46.0 | 55.9 | 56.1 | 67.8 | 66.2 | 59.7 | 59.3 | 62.0 | 60.1 | 57.1 | 55.6 |

**s.d.**

| 0.9 | 8.3 | 7.5 | 6.2 | 5.6 | 6.9 | 7.2 | 6.7 | 5.7 | 4.6 | 5.0 | 3.9 | 3.6 | 3.0 | 4.4 | 4.3 | 6.0 | 5.6 | 9.1 | 8.4 | 6.0 | 5.8 | 5.7 | 5.8 |

**Confidence interval**

| 5.1 | 4.6 | 3.8 | 3.5 | 4.3 | 4.5 | 4.1 | 3.5 | 2.8 | 3.1 | 2.4 | 2.2 | 1.8 | 2.7 | 2.7 | 3.7 | 4.1 | 5.6 | 5.2 | 3.7 | 3.6 | 3.8 |

**Percentage**

| 10% | 9% | 7% | 7% | 8% | 7% | 7% | 7% | 6% | 5% | 4% | 5% | 5% | 5% | 6% | 9% | 9% | 6% | 6% | 6% | 6% |

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**The CBF values are expressed in ml/100 g/min (L = left hemisphere and R = right hemisphere). The numbers corresponding to the ROIs are given in Figure 1.**
immunodepression. Three subjects had T4 lymphocyte counts above 500/mm$^3$, twelve subjects had counts of 500-200/mm$^3$, and three subjects had counts of $\leq$200. Subject 11 had close to 100/mm$^3$ (Table 1). Most of the subjects had cutaneous anergia, as the intradermal tuberculin reaction was negative in all cases. This fact is particularly significant for young French nationals because they had all undergone obligatory tuberculosis vaccination. There may be a question for Patient 11, aged 68, and for the two women of African origin.

MR Imaging. The results were normal in 14 cases and abnormal in 2 (Cases 2 and 11); two subjects were not examined. The two abnormal cases had hyperintense areas in T2-weighted MRI images in the periventricular white matter. No patients had cerebral atrophy.

EEG. Minor diffuse acute abnormalities were found in two cases, caused by hyperpnea (Case 3) or by intermittent light stimulation (Case 16).

Psychometric Tests. The overall performance of the group was good, with restricted and/or sudden disturbances. There were no praxic problems and visual-motor coordination was good. Certain subjects had difficulties with mental calculation and digit span (Cases 4, 10, 15, 16, 18) and symbolic thinking difficulties (Cases 2, 10, 14, 15, 16, 18). This type of problem seems to be an essential characteristic of the group studied. Memorization of verbal or graphic data was good or very good, but showed sudden discontinuities, as in subject 6 (reiterative sequence), subject 8 (complete loss of delayed recall), and subject 18 (complete loss of delayed recall and fabulation).

DISCUSSION

In this study, SPECT has been used to examine the abnormalities of cerebral perfusion in asymptomatic HIV-seropositive subjects. There are two points concerning the methodology which merit comment. First, the way in which the HIV-seropositive subjects were compared to the controls. It appeared very likely that the cerebral disorders of the HIV-1 seropositive subjects would vary from one individual to another. We therefore compared the regional values for each individual subject with the mean values for the control group, using 95% confidence limits to assess differences. Local or global interhemispheric asymmetries were considered significant if they differed from the control values by 10% or more, the maximum percent variation in normal subjects.

Second, the mean ages of the controls and HIV-positive subjects are different. While this difference is considerable, it does not, in itself, invalidate the comparison of rCBF values. There is good evidence that the mean hemispheric rBF does not vary with age between

![Figure 2](https://jnm.snmjournals.org/article-figures/02fig2.jpg)

**Figure 2** Perfusion abnormalities in two HIV-1 seropositive asymptomatic subjects. The white arrows indicate the areas of abnormal local hypoperfusion. Orientation is indicated on the left. (A) Crossed cerebral-cerebellar abnormalities, indicating a cerebral-cerebellar diaschisis (Patient 1). (B) Slice through OM + 5 cm, showing an overall reduction in cerebral perfusion mainly in the occipital regions (Patient 17).

![Figure 3](https://jnm.snmjournals.org/article-figures/03fig3.jpg)

**Figure 3** Percent abnormalities in each ROI. The regions containing unilateral or bilateral perfusion abnormalities are: frontal (77%), temporal (55%), parietal (44%), occipital (61%), thalamus (61%), and cerebellum (61%).
TABLE 2

Characteristics and Findings in HIV-1 Seropositive Asymptomatic Patients

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age</th>
<th>Sex</th>
<th>Psychometric tests</th>
<th>T4</th>
<th>T8</th>
<th>T4/T8</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 BAD.</td>
<td>31</td>
<td>F</td>
<td>N</td>
<td>&gt;300</td>
<td>&gt;600</td>
<td>&gt;0.5</td>
<td>ND</td>
</tr>
<tr>
<td>2 BER.</td>
<td>32</td>
<td>M</td>
<td>Slight cognitive dysfunction</td>
<td>345</td>
<td>252</td>
<td>1.36</td>
<td>Leukoencephalopathy</td>
</tr>
<tr>
<td>3 BOU.</td>
<td>32</td>
<td>M</td>
<td>N</td>
<td>362</td>
<td>1055</td>
<td>0.34</td>
<td>N</td>
</tr>
<tr>
<td>4 BUR.</td>
<td>27</td>
<td>M</td>
<td>Number memorization impairment</td>
<td>399</td>
<td>1302</td>
<td>0.31</td>
<td>N</td>
</tr>
<tr>
<td>5 COL.</td>
<td>28</td>
<td>M</td>
<td>N</td>
<td>736</td>
<td>511</td>
<td>1.44</td>
<td>N</td>
</tr>
<tr>
<td>6 DAR.</td>
<td>28</td>
<td>M</td>
<td>Mainly learning disorders</td>
<td>410</td>
<td>410</td>
<td>1.00</td>
<td>N</td>
</tr>
<tr>
<td>7 FAU.</td>
<td>37</td>
<td>M</td>
<td>N</td>
<td>192</td>
<td>1094</td>
<td>0.18</td>
<td>N</td>
</tr>
<tr>
<td>8 HUM.</td>
<td>26</td>
<td>M</td>
<td>N</td>
<td>432</td>
<td>454</td>
<td>0.95</td>
<td>N</td>
</tr>
<tr>
<td>9 JUN.</td>
<td>30</td>
<td>F</td>
<td>N</td>
<td>592</td>
<td>504</td>
<td>1.17</td>
<td>N</td>
</tr>
<tr>
<td>10 LAI.</td>
<td>24</td>
<td>M</td>
<td>Number memorization impairment</td>
<td>432</td>
<td>630</td>
<td>0.69</td>
<td>ND</td>
</tr>
<tr>
<td>11 LEM.</td>
<td>68</td>
<td>M</td>
<td>N</td>
<td>108</td>
<td>530</td>
<td>0.20</td>
<td>Leukoencephalopathy</td>
</tr>
<tr>
<td>12 MAR.</td>
<td>38</td>
<td>M</td>
<td>N</td>
<td>381</td>
<td>621</td>
<td>0.61</td>
<td>N</td>
</tr>
<tr>
<td>13 MIN.</td>
<td>34</td>
<td>M</td>
<td>N</td>
<td>260</td>
<td>451</td>
<td>0.58</td>
<td>N</td>
</tr>
<tr>
<td>14 PIQ.</td>
<td>31</td>
<td>M</td>
<td>Partial cognitive dysfunction</td>
<td>442</td>
<td>1082</td>
<td>0.41</td>
<td>N</td>
</tr>
<tr>
<td>15 RAJ.</td>
<td>40</td>
<td>M</td>
<td>Number memorization impairment</td>
<td>458</td>
<td>433</td>
<td>1.06</td>
<td>N</td>
</tr>
<tr>
<td>16 RIN.</td>
<td>28</td>
<td>M</td>
<td>Partial cognitive dysfunction</td>
<td>836</td>
<td>1227</td>
<td>0.68</td>
<td>N</td>
</tr>
<tr>
<td>17 VAL.</td>
<td>29</td>
<td>M</td>
<td>Visuo-spatial dysfunction</td>
<td>208</td>
<td>374</td>
<td>0.56</td>
<td>N</td>
</tr>
<tr>
<td>18 TRA.</td>
<td>25</td>
<td>M</td>
<td>Memory impairment</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>N</td>
</tr>
</tbody>
</table>

*Normal values (25).
N = normal; ND = not done.

The second and fifth decades (27,28). Some workers (29) believe that CBF may not be reduced even beyond that age in subjects having no vascular risk factors.

The major findings at this stage of the disease development were frequent abnormalities (88% of cases), which included regional interhemispheric asymmetry and/or an overall reduction in blood flow.

This frequency contrasts with the small number of disturbances shown by the data from most of the other tests. The clinical examination results were completely normal. The laboratory tests, especially the T4 and T8 lymphocyte counts, whose predictive significance in this disease is known (30), showed no correlation with the presence or absence of disturbances of cerebral perfusion. The MRI was abnormal in only two cases. There were small, diffuse disturbances in the EEG in two cases, with no topographic correlation with the SPECT results, reflecting the subcortical nature of the CBF disturbance. The psychometric tests were the only ones which showed frequent abnormalities (55% of cases). There were mainly sectorial cognitive problems and minor mnesic disturbances, which are always difficult to correlate with the data of seroconversion.

It is difficult to compare our data with those of others since there have been few studies on Phase II seropositive subjects. Only Trotot et al. (18) studied these abnormalities by MRI in 25 asymptomatic HIV-positive patients. They found abnormal cases (36%), eight with hyperintense areas in T2-weighted MR images of the periventricular white matter, and one case of cortical atrophy. Only 11% of anomalies were found by MRI in the present study. The difference is even larger when the abnormalities detected by the 133Xe-SPECT are considered.

MRI has proved to be much more sensitive than CT for detecting cerebral abnormalities due to opportunistic infections. The recent use of gadolinium-DTPA may increase the sensitivity and specificity of MRI (20). However, its performance is less impressive than that of emission tomographic methods for detecting the lesions of AIDS-complex dementia. Navia et al. (13) studied four subjects suffering from AIDS complex dementia by PET. They found hypometabolism only in the temporal lobes, mainly in the medial region. Brunetti et al. (14) showed, using the same method on four patients, one generalized low cortical glucose metabolism, two cases in which the bilateral abnormalities were either temporo-occipital or frontal, and one case of frontal-temporal damage with contralateral hypometabolism, causing crossed-cerebellar diaschisis.
apart from its intrinsic interest, confirms the organic reality of defects in hemispheric perfusion. Pohl et al. (11) used SPECT to show that 12 patients with AIDS-associated subacute encephalopathy all had abnormal HMPAO and/or IMP binding (6 multiple abnormalities, 3 fronto-basal, 1 fronto-temporal, 1 parieto-temporal, 1 occipital). CT scans detected 8 cases of cortical atrophy out of 12, while MRI detected leukoencephalopathic lesions in 2 out of 5 patients examined.

The frequency of perfusion abnormalities found in our study is broadly similar to that of the anatomic lesions found in patients who have died from AIDS. De la Monte et al. (5) examined 30 such patients and showed that the most frequent cerebral lesions were: temporal (69%), frontal (58%), occipital (52%), parietal (48%), basal ganglia (77%), and thalamus (58%). The percent cerebellar abnormalities (61%) found in the present study is significantly different from that found by De la Monte (22%). The association of functional CCD and organic cerebellar abnormalities may explain the high percentage found in our study. The hippocampal and amygdalial regions were found to be frequently damaged by De la Monte; these could not be individually distinguished by our technique and are included in the temporal and sylvian regions. But this type of topographic comparison can only be relative, except for the study of Trotot et al. (18), because of differences in the stage of the disease and the methods used.

The major question arising from this study is that of the pathophysiology of the circulatory disturbances found in these asymptomatic seropositive subjects. The virus seems to penetrate the CNS via macrophages and monocytes, which can cross the blood-brain barrier (31). Once it is within the brain, the virus binds to CD4 receptors or analogous structures. There are several possible explanations for the disturbances in CBF found in this study. Direct neuronal damage by HIV (2,32), the toxic effects of enzymes secreted by infected cells (4,33), or a reduction in trophic factors (34) may all reduce CBF. White matter damage, which occurs frequently in AIDS (5,8), may also cause local reductions in cerebral perfusion. Local demyelination probably occurred in the two of our subjects who had abnormal MRI, with hyperintense areas in T2-weighted MR images of the periventricular white matter reminiscent of sclerotic plaque lesions (18). Demyelination would result from an autoimmune reaction by cells antigenically modified by virus binding, as described in the peripheral nervous system (35). This demyelination could also result in a reduction in glial vasoactive intestinal peptide (VIP) secretion (36). This neuromediator has a trophic action on neurones and acts as a vasodilator on cerebral vessels. A recent study (34) showed that there were similarities between the virus envelope T molecule and VIP. Thus, the virus may be acting as a VIP antagonist. Direct vascular damage may occur by HIV infecting the cerebral vessel endothelial cells, causing local rupture of the blood-brain barrier (8,37), and increasing the sensitivity of arteriolar smooth muscles to catecholamines (38). Perivascular inflammation, which is frequently found in cephalic arterioles (4,5,9,39) or arterioles in the white matter and central grey nuclei (7), is aggravated by the secretion of certain enzymes by infected macrophages (33). Finally, opportunistic infection in the CNS is possible, but may be excluded in our study. There were no focal clinical signs of encephalopathy, the MRI was normal in 16 cases, with the appearance of focal demyelination in the remaining two. There was no significant immunodepression, with the T4 counts being normal or subnormal except in Case 11, where it was very low.

The results of this study show that abnormal cerebral perfusion is frequent (88% of cases) in the early stages of HIV-1 infection. The abnormalities are most often found in the frontal lobe (77% of cases), the occipital lobe, and the thalamus and cerebellum (66% of cases). The temporal (55%) and parietal (44%) lobes are less frequently involved. The other methods used to detect brain abnormalities tend to reveal fewer disturbances than does SPECT. MRI showed just two abnormalities, while the psychometric tests indicated discrete mnestic and gnomic disturbances. EEG showed few nonspecific abnormalities.

It would be unwise to extrapolate these results for a selected group of subjects to all HIV-seropositive subjects. Nevertheless, they clearly demonstrate that quantitative measurement of CBF by 133Xe-SPECT, which is a readily performed routine analytical method, can be used to detect early changes in Phase II HIV-seropositive subjects. The method may also be suitable for monitoring the therapy of cerebral forms of AIDS. However, only a longitudinal study of these patients can provide suitable answers to these questions.

REFERENCES

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