Cerebral Vasculopathy in HIV Infection Revealed by Transcranial Doppler
A Pilot Study

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Background and Purpose—There is growing evidence for affection of cerebral vessels during human immunodeficiency virus (HIV) infection. We prospectively evaluated cerebrovascular reserve capacity (CRC) in HIV-seropositive patients by transcranial Doppler sonography (TCD) after systemic administration of acetazolamide. We hypothesized that a disturbed vasoreactivity would reflect the cerebral arteries’ involvement in HIV infection.

Methods—We assessed the mean blood flow velocity (BFV) of the middle cerebral artery and its increase after intravenous administration of 1 g acetazolamide (CRC) in 31 HIV-infected individuals without symptoms of cerebrovascular disease (mean ± SD age, 39 ± 11 years). Stenotic or occlusive lesions of the large brain-supplying arteries were excluded by color-coded duplex and transcranial imaging. BFV and CRC were also measured in an age-matched group of 10 healthy control subjects. Patients were classified according to clinical, laboratory, and neurophysiological parameters. We also performed cerebral MRI (n = 25) and rheumatological blood tests (n = 26).

Results—Baseline BFV and CRC both were significantly reduced in HIV-infected patients as compared with control subjects (P < 0.05, Student’s t test). These findings did not correlate with duration of seropositivity, helper cell count, or other clinical, rheumatological, and neuroradiological findings.

Conclusions—Our findings support the hypothesis of a cerebral vasculopathy etiologically associated with HIV infection. (Stroke. 1999;30:811-813.)

Key Words: cerebrovascular circulation ■ cerebral vasculopathy ■ HIV ■ ultrasonography, Doppler, transcranial

There is a large spectrum of neurological disorders associated with the human immunodeficiency virus (HIV) infection.1,2 Two main pathogenetic mechanisms for the involvement of the central nervous system (CNS) are discussed: 1 is a direct interaction of CNS cells with HIV, the other 1 is opportunistic infections or neoplasms due to the progressive immunodeficiency.1,2 There is also clinical and histopathological evidence suggesting that HIV infection may cause a variety of inflammatory vascular diseases.3 Cerebral vasculitis during HIV infection and AIDS has been found in postmortem examinations.4–6 Furthermore, 133Xe single-photon emission-computed tomography (SPECT) revealed abnormalities of cerebral perfusion in asymptomatic HIV-positive subjects.7 Affection of the cerebral microcirculation and its blood-brain barrier has been reported, the role of this affection in the pathogenesis of HIV-encephalopathy is under debate.8–10 The overall clinical relevance of these vasculopathies is still unclear. There are several reports on stroke during HIV infection (eg, References 11 and 12), and the incidence of stroke in HIV-positive subjects appeared to be higher as compared with noninfected controls; however, to date it has been impossible to give statistical proof for that observation.13

We performed this study to evaluate the cerebrovascular reserve capacity (CRC) in 31 HIV-infected individuals without symptoms of cerebrovascular disease. Our aim was to assess whether there is already evidence for cerebral vasculopathy in these individuals and whether these changes are related to clinical, rheumatological, neurophysiological, or neuroradiological findings.

Subjects and Methods
We included 31 HIV-positive outpatients, 3 women and 28 men, without signs for current infection or cardiovascular or respiratory disease. No patient had a history of CNS infection or signs of cerebrovascular disease. Mean age was 39 ± 11 years (range, 23 to 59 years), and mean duration of HIV infection (ie, known seropositivity) was 4.0 ± 3.4 years (range, 1 month to 12 years). The clinical stage according to the Centers for Disease Control and Prevention (CDC) criteria14 could be defined in 29 patients: 6 subjects were classified as CDC A, 16 as CDC B, and 7 as CDC C (AIDS). In all but 2 patients, a recent helper cell count was either known or had been performed by us; mean helper cell count (ie, CD4+ lymphocytes) was 217 ± 169 per μL. Eight patients had a probable minor
cognitive disorder according to the criteria of the American Academy of Neurology AIDS Task Force.15 The minor cognitive disorder was confirmed by delayed latencies of event-related potentials. None had definite signs of HIV-1–associated dementia complex. Electroneurography (peroneal nerve motor conduction and sural nerve sensory conduction) was performed in all but 4 patients; a polyneuropathy, either symptomatic or asymptomatic, was diagnosed in 19 patients. A blood sample was taken for helper cell count, examination of c-reactive protein, rheumatoid factor, Rose-Waaler test, antinuclear antibodies, anticitrullinated antibodies (IgGM), and circulating immunocomplexes (n = 26) to exclude possible autoimmune vasculitis. MRI scan of the brain was performed in all but 6 patients. Three of these dropouts did not show up to the appointment, and 3 did not consent because of claustrophobia. We used axial T2-weighted and coronal T1-weighted spin-echo sequences. In 2 patients, a CT of the head was performed instead of an MRI. Color-coded duplex imaging of the neck arteries (HP Sonos 2500, Hewlett Packard) and transcranial Doppler ultrasonography (TCD) of intracranial arteries were performed in all patients. We used TCD also after administration of acetazolamide according to Piepgras et al.6 The middle cerebral arteries were sonicated at a depth of between 45 and 55 mm through the temporal bone window. The correct identification of the arteries was performed according to the literature.17 The probes were fixed bilaterally by a headband.

All patients or volunteers had given informed consent before injection, and allergy to sulfonamides, electrolyte disorder, and hyperuricemia had been excluded a priori by questionnaire and laboratory testing. Administration of acetazolamide and functional TCD were performed in a standardized setting: the mean blood flow velocity (BFV) of the middle cerebral artery was registered at rest and at 5-minute intervals after acetazolamide application. Acetazolamide (1 g) was dissolved in 10 mL H2O and injected within 2 minutes in an antecubital vein via a prepared venous catheter. During the test, ventilation was observed, and the respiration rate remained stable in all patients. Blood pressure was measured in the lying position before and after the total procedure. BFV was evaluated bilaterally in all but 4 patients. The latter ones had only been registered unilaterally because of technical reasons (n = 3) or lacked a temporal window (n = 1; a 59-year-old patient). All TCD examinations were done with the same TCD unit (Multi Dop X, DWL) and were performed by the same examiner (R.B.).

We also performed bilateral TCD before and after acetazolamide application in a control group of 10 healthy volunteers (age 34 ± 14 years, difference to patient group not significant). Results are reported as arithmetic mean and simple SD, statistical comparisons were performed by the same examiner (R.B.).

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Results

C-reactive protein was slightly elevated in 6 patients, rheumatoid factor and Rose-Waaler tests were all negative. Antinuclear antibodies were positive in 10 patients, their quantity was elevated in only 1 patient. We found circulating immunocomplexes in 5 patients.

Twenty patients had elevated anticitrullinated antibodies of the IgG type (mean, 25.4 ± 20.5 U/L), whereas anticitrullinated of the IgM type was abnormal in only 5 patients (mean, 3.5 ± 3.9 U/L). Color-coded duplex imaging was normal in all but one 59-year-old patient who had nonstenosing atherosclerotic plaques without hemodynamic relevance. We did not find any abnormalities in CT scan. MR images (n = 25) were also normal except for 5: in 3 patients, we observed a few small hyperintense signal abnormalities in the white matter of both hemispheres on T2-weighted images. Additionally, we detected 1 small hemangioma in the right internal capsule in 1 and a mild cerebral atrophy in another patient.

Each variable showed a z value above 0.5 in the Kolmogorov-Smirnov test, suggesting a parametric distribution. Therefore, Student’s t test was applied in the further analysis. BFV and their maximum increase after injection of acetazolamide (CRC) are given in Table. No significant hemispheric differences of baseline BFV or CRC and of blood pressure before and after the procedure were found, nor for the patient or control group. By contrast, baseline BFV and CRC were reduced in the HIV-infected group as compared with healthy control subjects, with significant differences on both sides (P < 0.05 for baseline BFV and P < 0.005 for CRC). The mean CRC (ie, the averaged relative increase of the right and left sides) was obtained in 27 patients, the results were 31% in HIV-infected patients and 47% in control subjects (P < 0.0002). We did not find any correlation between the reduced CRC and other HIV-specific, clinical, or laboratory parameters such as age, presence of polyneuropathy, duration of seropositivity, helper cell count, circulating immunocomplexes, and anticitrullinated or antinuclear antibodies. However, we observed a trend that the mean CRC was slightly more reduced in patients with AIDS (29%) as compared with earlier stages of HIV infection (33%). There was no significant difference in BFV and CRC between patients with and those without minor cognitive disorder.

Discussion

The rationale for this study was the growing evidence for the existence of HIV-associated peripheral and cerebral vasculopathies in the literature. Acetazolamide increases cerebral blood flow, presumably via vasodilation of small arterioles, and this effect may be used to assess cerebral vasoreactivity by means of TCD.18 To the best of our knowledge, we were the first to evaluate BFV and CRC after the administration of acetazolamide in HIV-infected patients. We found a significant reduction in baseline BFV and CRC in this clientele. None of our patients had a severe impairment of cardiac function or a stenosis of the brain-supplying arteries, which would explain reactive cerebral vasodilation. Therefore, it is likely that reduced BFV and CRC reflect alterations of cerebral resistance at the arteriolar level. Whether this vascular dysfunction is directly related to HIV infection or the result of other factors such as asymptomatic opportunistic

<table>
<thead>
<tr>
<th>Baseline BFV and CRC in HIV-Infected Individuals (n=31) and Healthy Control Subjects (n=10)</th>
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<tbody>
<tr>
<td><strong>Baseline BFV right MCA, cm/s</strong></td>
</tr>
<tr>
<td>HIV-Infected (n=31)</td>
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<tr>
<td>Controls (n=10)</td>
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<tr>
<td><strong>CRC right MCA, %</strong></td>
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<tr>
<td><strong>CRC left MCA, %</strong></td>
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<td><strong>Mean CRC of both MCA, %</strong></td>
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Data are presented as arithmetic mean and simple SD, statistical comparison by Student’s t test. Bilateral values were obtained only in 27 of 31 HIV-infected patients.

MCA indicates middle cerebral artery.
infection or medication remains to be determined. We did not find any clues concerning etiology and dignity of our findings because no correlation with any other parameter was found.

Decreased baseline BFV and reduced CRC after acetazolamide have also been reported in patients with non–HIV types of cerebral vasculitis, eg, systemic lupus erythematosus with CNS affection according to clinical and MRI findings. This has been interpreted as a sign of damage to brain vessel walls.20 Isaka et al reported decreased CRC in subjects with asymptomatic periventricular hyperintensities in MRI.21 Only 3 MRI scans in our cohort revealed these abnormalities. This is why the above findings cannot be explained according to Isaka et al.21

Disorders of the cerebral microcirculation in HIV infection have already been described by other authors,5–10 Power et al suggested a chronic progressive disease,10 but we could not find evidence for a relation of the reduced CRC to the duration or to parameters indicating the progression of HIV infection because we did not find a significant correlation to the helper cell count, a test of acknowledged predictive value in HIV infection,22 or to any other clinical feature of the cohort’s HIV disease. Similar to our results, abnormalities of the cerebral perfusion in asymptomatic HIV-positive patients revealed by 133Xe SPECT2 did not correlate to helper cell count, neuropsychological findings, or rare MRI abnormalities. The occurrence of a cerebral vasculopathy in HIV infection might thus be influenced by HIV-independent individual factors such as genetic or infectious predisposition.

In summary, we found evidence for a CNS vasculopathy in HIV-infected individuals without symptoms of cerebrovascular disease. This disorder seems to be confined to small cerebral arterioles or at least to the peripheral vascular bed. Further studies should be performed to investigate whether there is a correlation of reduced CRC with findings revealed by functional imaging techniques (such as SPECT or functional MRI) or neuropsychological testing. Furthermore, prospective follow-up studies are warranted to evaluate whether there is intraindividual progression and prognostic relevance of our findings in terms of the manifestation of cerebrovascular disease.

References

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