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Highly Active Antiretroviral Therapy for Patients with AIDS Dementia Complex: Effect on MR Imaging Findings and Clinical Course

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BACKGROUND AND PURPOSE: **Recent studies have reported the clinical improvement in patients with AIDS treated with a combination of antiretroviral regimens. The purpose of our study was to describe the effects of highly active antiretroviral therapy on MR images in patients with HIV encephalopathy and to compare the clinical course with follow-up neuroimaging studies.**

METHODS: **Initial and follow-up MR imaging findings are described in four patients with AIDS dementia complex at baseline and after antiretroviral therapy, and correlated with clinical and immunologic findings.**

RESULTS: **Initial MR imaging revealed white matter signal abnormalities on long-TR images without mass effect and without enhancement on postcontrast images, consistent with HIV encephalopathy. Lesions were located in the basal ganglia and posterior fossa in two patients. All four patients showed progression of white matter disease on the first follow-up MR scan (mean, 6 months). On subsequent scans, regression was seen in three patients and stabilization of white matter disease was observed in one patient. Increases in CD4+ count and decreases in viral load below the limit of quantification were present in all patients.**

CONCLUSION: **Although our patient population was small, the results suggest that disease regression in patients with AIDS dementia complex after treatment with highly active antiretroviral therapy can be characterized and monitored by MR imaging.**

AIDS dementia complex (ADC) is one of the most common and important causes of morbidity associated with infection by human immunodeficiency virus type 1 (HIV-1). It is attributed to cerebral HIV infection whose histopathologic marker is the presence of multinucleated giant cells. Two distinct histopathologic patterns have been recognized: HIV encephalitis, which is characterized by perivascular accumulations predominantly of microglia cells, monohistiocytes, and macrophages, and HIV leukoencephalopathy, which is characterized by the triad of diffuse myelin loss, astroglial proliferation, and infiltration by mono- and multinucleated macrophages (1, 2). HIV encephalitis and HIV encephalopathy can also be distinguished clinically and radiologically, and they probably represent distinct subtypes of ADC.

The most commonly reported MR imaging finding in patients with ADC is cerebral atrophy. A butterfly-like pattern of diffuse increase in white matter signal intensity on long-TR images has been observed in HIV leukoencephalopathy. In patients with HIV encephalitis, patchy areas of high signal intensity have been described on T2-weighted sequences (3–7).

An increased knowledge of the pathogenesis of HIV, the development of sensitive measurements for such viral parameters as viral load determinations, and the availability of new classes of antiretroviral drugs—eg, the protease inhibitors and the nonnucleoside reverse-transcriptase inhibitors (NNRTI)—have profoundly improved the therapeutic management of HIV infection (8–13). Various combinations of antiretroviral drugs, often but not always including one protease inhibitor and two nucleoside reverse-transcriptase inhibitors (NRTI), have been shown to increase CD4+ lymphocyte counts and to decrease viral replication in plasma and lymph nodes to undetectable levels. In the past 3 years, the widespread implementation of this

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TABLE 1: Drug regimens in four patients with AIDS dementia complex

		Reverse Transcriptase Inhibitors		Protease Inhibitors
Patient No.	Age (y)/Sex	NRTI, Dose	NNRTI, Dose	PI, Dose
1	56/M	ZDV, 250 BID 3TC, 150 BID	NVP, 200 BID	IDV, 1000 TID
2	53/M	ZDV, 250 BID 3TC, 150 BID	NVP, 200 BID	IDV, 1000 TID
3	31/F	ZDV, 250 BID 3TC, 150 BID	NVP, 200 BID	NFV, 1250 BID
4	43/M	3TC, 300 OD* ddI, 250 OD*	NVP, 400 OD*	
		dT4, 30 BID ddI, 125 BID		IDV, 800 TID

Note.—NRTI indicates nucleoside reverse-transcriptase inhibitors; NNRTI, nonnocleoside reverse-transcriptase inhibitors; PI, protease inhi bitors; ZDV, zidovudine; 3TC, lamivudine; ddI, didanosine; dT4, stavudine; NVP, nevirapine; IDV, indinavir; NFV, nelfinavir; BID, twice a day; TID, three times a day; OD, once a day.

* Drug regimen without PI (4 months).

highly active antiretroviral therapy (HAART) has resulted in dramatic decreases in AIDS-related morbidity and mortality. Nevertheless, little information is available on the effects of HAART in patients with ADC in regard to clinical status or neuroradiologic changes or both (14). The aim of our study was to characterize the imaging findings after HAART in four patients with ADC and to compare their clinical course with initial and follow-up MR studies.

Methods

Four patients, three men and one woman (31–56 years old; mean age, 46 years) with ADC, who received HAART were included in the study. One patient was homosexual, one was a drug abuser, one had been infected by a blood transfusion, and one was living in an endemic area. The diagnosis of AIDS was made according to the criteria established by the Centers for Disease Control and was based on clinical, neuropsychological, and imaging findings. The patients received quadruple combination antiretroviral therapy, consisting of three transcriptase inhibitors and one protease inhibitor. Table 1 shows the drug regimens of the patients.

Three patients had not received prior antiretroviral therapy and were compliant with current medication regimens. Because of poor compliance in one patient, an experimental once-daily administered drug regimen was initiated, consisting of an NNRTI (nevirapine) and two NRTIs (didanosine and 3TC). Owing to persistent viral replication 5 months later, the antiretroviral regimen was modified to a combination consisting of the protease inhibitor indinavir plus two NRTIs, didanosine and stavudine plus hydroxyurea, a cytostatic drug that enhances the antiretroviral efficacy of NRTIs.

The MR examinations were performed on a 1.0-T or a 1.5-T superconducting system using a circularly polarized head coil. Axial T1-weighted spin-echo (SE), T2-weighted fast SE (FSE), and fluid-attenuated inversion-recovery (FLAIR) FSE sequences were obtained. Gadopentetate dimeglumine was administered as an intravenous bolus injection (0.1 mmol/kg body weight) for contrast-enhanced T1-weighted studies in all patients. We used a section thickness of 4 to 6 mm, an intersection gap of 1 mm, a field of view of 230 mm with a 70% rectangular field of view, and an image matrix of 192 × 256 pixels. TR/TE parameters on the 1.0-T (1.5-T) system for the T1-weighted SE sequences were 550 (488)/20 (15). For the T2-weighted FSE sequences, we used a TR of 4545 (5400) and a TE_{eff} of 100 (130), and for the FLAIR sequences an inversion recovery time (TI) of 2100 (2600) and a TR of 10000 (9000).

Follow-up MR studies were performed after 1.5 to 22 months of therapy. Two patients had three follow-up MR studies and two patients had two follow-up examinations. The first follow-up studies were performed after 1.5 to 9 months (mean, 6 months), the second after 6 to 15 months (mean, 10.6 months), and the last after 18 to 22 months (mean, 20 months) of antiretroviral therapy.

Each MR image was reviewed with respect to the pattern of white matter signal intensity abnormalities (multifocal/diffuse), the severity of white matter abnormalities (mild, moderate, severe), and whether the white matter abnormalities were stable, had worsened, or had improved in the interim. Less than 25% involvement of the white matter was graded as mild, 25% to 75% as moderate, and greater than 75% was considered severe. In addition, signal intensity abnormalities within the basal ganglia and posterior fossa were also assessed for any interval change on follow-up MR images.

In all patients, the presence or absence of atrophy was subjectively noted, and discrepancies in interpretation were resolved by consensus. Atrophy was defined as inappropriately prominent ventricles and cortical sulci for the patients' age. Atrophy was also graded as mild, moderate, or severe.

For follow-up MR studies, the degree of white matter signal intensity abnormalities on long-TR images and the degree of atrophy was compared with the initial studies. The initial and follow-up MR images were evaluated individually by two experienced neuroradiologists, who then reviewed the cases together to reach a consensus.

Medical records were reviewed for neurologic signs and symptoms, CSF analysis, CD4+ T-lymphocyte counts (cells per mm^3), and HIV-1 RNA level (viral load, copies per millimeter) before (baseline) and during therapy.

Results

Initial MR Imaging Findings

On the initial MR studies, one patient had mild white matter disease, one had moderate disease, and two had severe disease. On T2-weighted and FLAIR sequences, high signal abnormalities were present bilaterally in the periventricular white matter in all patients. On T1-weighted images the lesions were isointense. Additionally, in one patient

the lesions were located on the right side of the pons and in the cerebral peduncles on both sides. Another patient had high signal abnormalities on long-TR images in the midbrain (Fig 1). Basal ganglia lesions were present in two patients: one patient had lesions in the left thalamus and in both lenticular nuclei. Another patient had signal intensity abnormalities in the right caudate nucleus and in both thalami (Fig 2).

The white matter signal intensity abnormalities were multifocal in two patients and diffuse in the other two. None of the patients had a focal mass lesion or areas of abnormal enhancement on contrast-enhanced images. Cerebral atrophy was present initially in three patients, which was judged to be mild in one and moderate in two.

Follow-up MR Imaging Findings

The imaging findings of the initial and follow-up MR studies are summarized in Table 2.

In one patient (case 1), the first follow-up MR image 9 months after therapy showed increased white matter signal intensity abnormalities. On the subsequent examinations, 15 and 22 months after initiation of the therapy, no interval change was observed (Fig 1). Progression of the signal abnormalities evident on the first follow-up MR study were also observed in another patient (case 2). The MR study obtained 9 months after the initiation of antiretroviral therapy showed mild progression of white matter disease. On follow-up MR images, at 11 and 18 months, regression of the abnormality was observed.

In patient 3, worsening of the white matter disease, as well as development of atrophy, was observed on MR images 1.5 months after the initiation of therapy. Regression of the white matter abnormalities and complete resolution of the hyperintensities in the basal ganglia were apparent on the 7.5-month follow-up study (Fig 2).

In patient 4, the first follow-up MR study, 4 months after the beginning of therapy without protease inhibitors, showed resolution of the lesions in the basal ganglia and the posterior fossa, and progression of the white matter signal abnormalities. Six months after the initiation of protease inhibitor therapy, however, the follow-up study showed slight regression of the white matter disease.

In all patients, the first follow-up MR study (mean, 6 months after the initiation of therapy) showed a progression of cerebral white matter disease. On subsequent, sequential MR examinations, regression or stability of the signal abnormalities was observed. Lesions located in the basal ganglia region and in the midbrain showed regression or complete resolution at the first follow-up study.

Progression of the atrophy was observed in three patients on follow-up MR images. In one patient (case 1), atrophy progressed from mild to severe on the first follow-up study. On subsequent MR images, no change in atrophy was observed. In the patient in whom no atrophy was seen on the first study (pretreatment MR image) (case 3), mild atrophy could be seen on the first follow-up study with further progression of the ventricular enlargement on the second follow-up examination. In another patient (case 4), atrophy was graded as moderate on the initial MR study, and progressed slightly with ventricular dilatation. No change in atrophy over time was seen in one patient (case 2).

A comparison of the initial (pretreatment) findings with the last follow-up examinations revealed an increase in white matter signal intensity abnormalities in two patients. In the other two patients, the white matter signal intensity abnormalities, which had increased on the first follow-up examinations, had regressed and were graded the same as those on the initial study.

Neurologic and Neuropsychological Findings

Gait difficulty and lower extremity weakness were present in two patients each (cases 2 and 4). One patient had headache (case 3), and in one patient depressive symptoms were present (case 1). Impairment in concentration, memory, and orientation was observed in two patients (cases 1 and 4). Mental slowing was described in one patient (case 3). Neurologic examination was normal in one patient (case 3), one patient had positive pyramidal signs (case 2), and one patient was tetraspastic (case 4). Increased tone of the upper and lower extremities and tremor were present in one patient (case 1). Neuropsychological testing was consistent with a subcortical type of dementia in all patients. Improvement in clinical symptoms and mental status after the initiation of therapy was observed in all patients.

Immunologic Findings

In all patients, an increase in the CD4+ count (pretreatment mean value of the CD4+ count was 99.8, posttreatment mean value was 377) and a decrease in the HIV viral load below the limit of quantification was observed during the therapy. An HIV RNA level of less than 0.5×10^2 copies per milliliter was considered to be below the limit of quantification. In patient 4, the follow-up CD4+ cell response (before initiation of therapy, the CD4+ count was 32, after 8 months of therapy it was 72) may have been blunted by the addition of hydroxyurea.

CSF Analysis

Lumbar puncture was performed in two patients. The CSF analysis in one of the patients (case 3) showed a viral load of 2.2×10^5 copies per milliliter, and 314 cells (predominantly lymphocytes). Three weeks after the start of antiretroviral combination therapy, repeat CSF analysis showed a decrease in HIV-1 RNA viral load level (6.1×10^2 copies per milliliter) and cell count (92 cells). The last CSF ex-

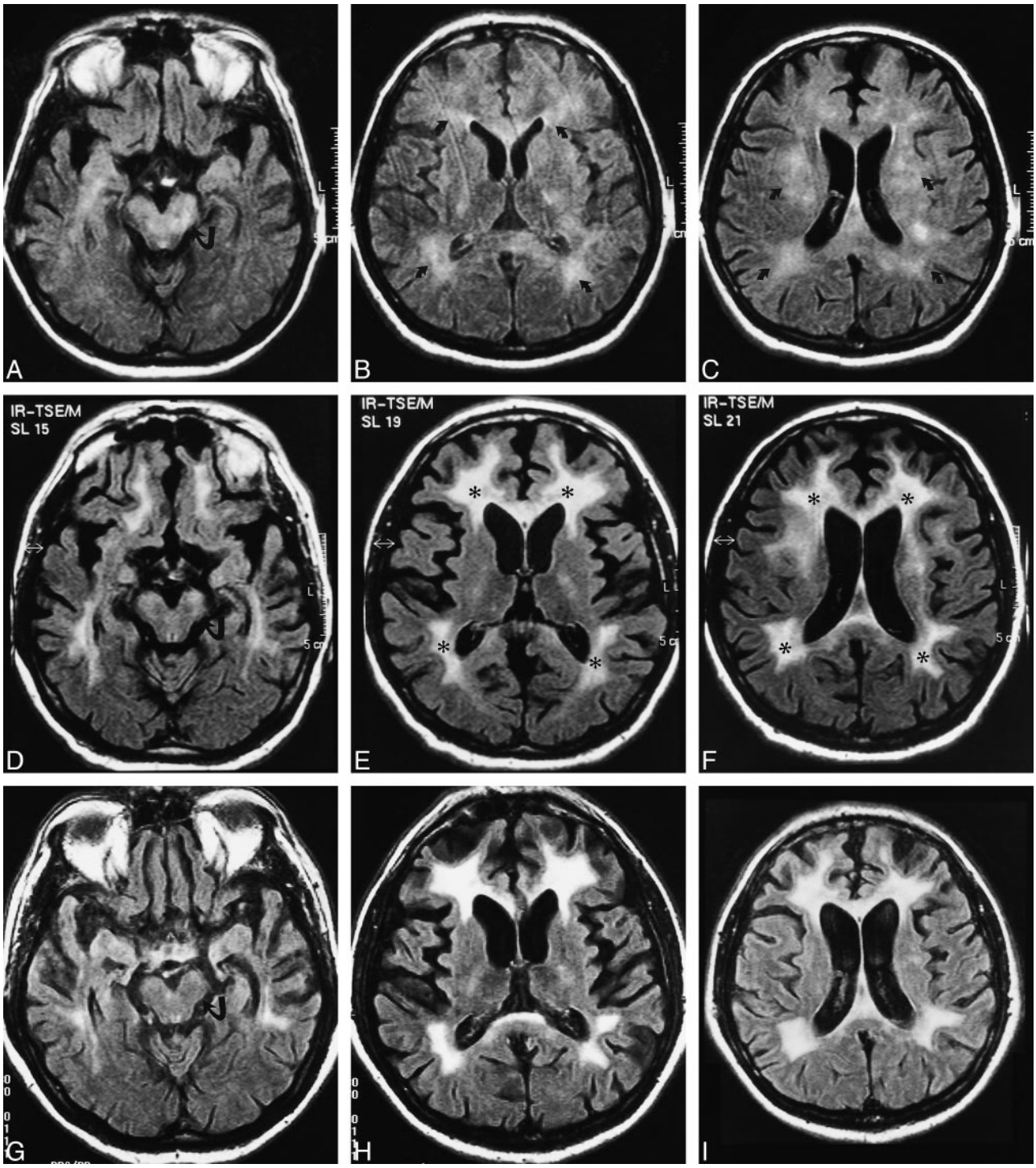

FIG 1. MR findings in a 56-year-old man (patient 1) with HIV-leukoencephalopathy being treated with a combination therapy of nonnucleoside analogues and protease inhibitors. He presented with impairment in concentration and memory and depressive symptoms. Neuropsychological testing was consistent with subcortical dementia.

A–C, TSE-FLAIR (7374/130, TI = 2100) images show symmetric regions of abnormally increased signal intensity (*arrows, B* and *C*) without mass effect in the periventricular white matter bilaterally. Additionally, high signal intensity was observed in the midbrain (*arrow, A*) and left cerebral peduncle.

D–F, Nine months after the initiation of therapy, follow-up TSE-FLAIR (7374/130, TI = 2100) images show interval increase in the hyperintense signal abnormalities (*asterisks, E* and *F*) in the periventricular white matter and progression of the cerebral atrophy, as well as almost complete resolution of the signal abnormality in the midbrain (*arrow, D*). Neuropsychological testing revealed an improvement in mental status.

G–I, Subsequent TSE-FLAIR (9000/105, TI = 2370) images of the brain 22 months after start of treatment show no interval change in distribution or severity of the white matter abnormalities, and complete resolution of the signal abnormality in the midbrain (*arrow, G*).

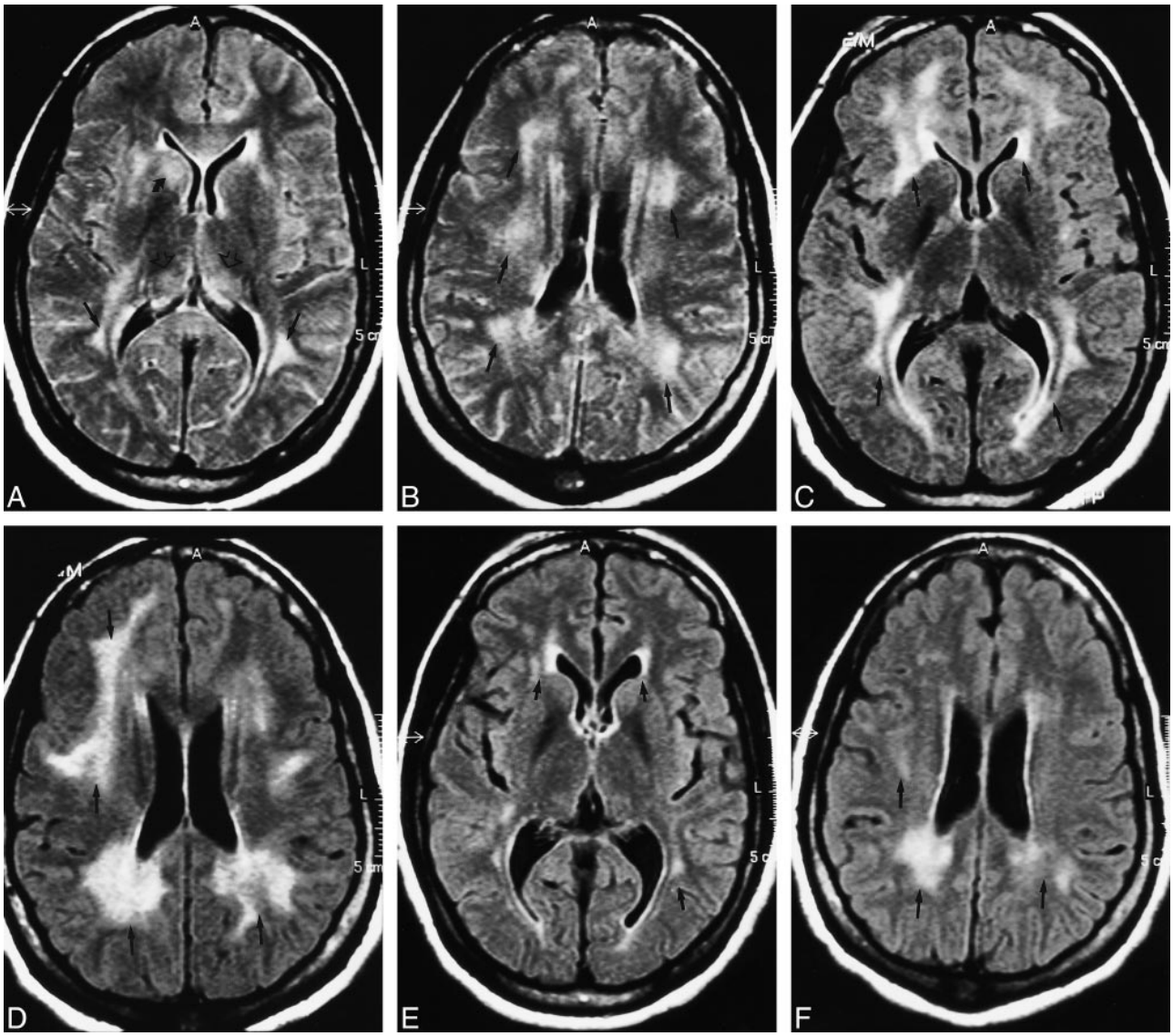

FIG 2. MR findings in a 31-year-old woman (patient 3) with AIDS who presented initially with headache, slowing of thoughts, aphasia, and impairment in memory. HIV-1 RNA assay revealed high viral load in serum and CSF. Imaging findings were consistent with HIV encephalitis. HAART, including one protease inhibitor, was started.

A and *B,* Pretreatment axial FSE-FLAIR images (10000/150, TI = 2600) show areas of increased signal intensity at the anterior portions of the external capsules bilaterally, in the right caudate nucleus (*curved arrow, A*), and periventricular white matter in the frontal, parietooccipital, and central areas bilaterally (*straight arrows*). Additional lesions are present in both thalami (*open arrows, A*).

C and *D,* Six weeks after the initiation of HAART, including protease inhibitors, corresponding axial FSE-FLAIR images (7374/130, TI = 2100) show resolution of the signal intensity abnormalities in the basal ganglia and thalami (*C*) but progression of the white matter abnormalities (*arrows*). The patient had improved clinically at that time.

E and *F,* Seven months after the start of a potent antiretroviral therapy regimen, axial FSE-FLAIR images (7385/130, TI = 2100) at the same level show an interval decrease in the high signal abnormalities within the occipital, parietal (*arrows, F*), and frontal (*arrows, E*) white matter.

amination, 7 months later, showed normal findings (viral load was less than 0.5×10^2 copies per milliliter, cell count was 3). In another patient (case 4), CSF analysis showed 613 cells and an HIV-1 RNA viral load of 3.5×10^5 copies per milliliter. A second lumbar puncture was not performed.

Comparison between MR Imaging Findings and Immunologic Status

In all four patients there was a discrepancy between MR findings on the first follow-up studies and immunologic status. Progression of the signal intensity abnormalities on MR images was followed by an increase in CD4+ count and a decrease in viral load level. On the second follow-up MR examination, one patient (case 1) showed stable findings and further improvement in immunologic status. In the other patients (cases 2, 3, and 4) regression of MR abnormalities and further improvement in immune function were observed. The evolution of the atrophic changes did not correspond to improvement in CD4+ count or clinical status.

TABLE 2: Initial and follow-up MR findings in four patients with AIDS dementia complex receiving highly active antiretroviral therapy

Patient No.	Age (y)/ Sex	Initial Study				Follow-up Studies											
						First Follow-up				Second Follow-up				Third Follow-up			
		WMD	BG	PF	Atrophy	Interval (mo)	WMD	BG	PF	Atrophy	Interval (mo)	WMD	BG	PF	Atrophy	Interval (mo)	WMD	BG	PF	Atrophy
1	56/M	++	0	+	+	9	+++	0	0	+++	15	+++	0	0	+++	22	+++	0	0	+++
2	53/M	+	0	0	++	9	++	0	0	++	11	++	0	0	++	18	+	0	0	++
3	31/F	++	+	0	–	1.5	+++	+	0	+	7.5	++	0	0	++	…	…	…	…	…
4	43/M	+++	+	+	++	4	+++	0	0	+++	10	++	0	0	+++	…	…	…	…	…

Note.—WMD indicates white matter disease; BG, basal ganglia; PF, posterior fossa; +, mild; ++, moderate; +++, severe; –, no abnormality.

In three patients a progression of the atrophy was observed on sequential MR studies despite improvement in immunologic and clinical status. Only in one patient (case 2) was no interval change in atrophy observed.

Discussion

ADC is characterized by disturbances in cognition, motor performance, and behavior (15). Patients report decreased concentration, forgetfulness, slowing of thought, loss of libido, apathy, inertia, and waning interest in work and hobbies, resulting in social withdrawal. Motor symptoms include clumsiness, tremor, unstable balance, gait disturbance, and slowing of rapidly alternating movements. The early symptoms are often subtle and may be confused with psychiatric complaints or overlooked. The clinical and neuropsychological abnormalities in ADC fit with the pattern of subcortical dementia. According to the original definition, subcortical dementia is characterized by forgetfulness, a slowing of mental processing, and intellectual deterioration (16). Attention, concentration, and language, which are typically related to cortical dysfunction, are usually not affected in ADC; however, on occasion, some of these patients may exhibit both subcortical and cortical dysfunction (17, 18).

Multifocal giant cell encephalitis and progressive diffuse leukoencephalopathy are neuropathologic correlates of cerebral infection with HIV (1, 2). Multifocal giant cell encephalitis is characterized by perivascular accumulations, predominantly of microglia cells, monohistiocytes, and macrophages. Progressive diffuse leukoencephalopathy is characterized by a triad of diffuse myelin loss, astroglial proliferation, and infiltration by mono- and multinucleated macrophages (1, 2). Glass et al (19) recently completed a prospective analysis of HIV dementia and found that only 25% of patients with ADC had multifocal giant cell encephalitis, and 50% showed neither multifocal giant cell encephalitis nor white matter pallor. Since HIV-1 does not infect neurons directly, indirect mechanisms (eg, triggered by HIV-infected CNS macrophages) may play a role in the pathogenesis of HIV dementia.

Radiologic studies are important in ADC patients to exclude other infections and tumors. Atrophy is the most common imaging finding in ADC (3). MR imaging abnormalities include multiple discrete foci, patchy areas of confluent involvement, or diffuse parenchymal involvement observed on long-TR images (4–7, 20). Olsen et al (5) found that the diffuse white matter pattern was the most common MR imaging finding in patients with ADC, with this pattern occurring in 70% of the patients in their study. In another study, the presence of white matter disease did not differ between patients with and without dementia (4). Several authors have claimed that neuroimaging studies are relatively insensitive in the detection of microglial nodules with multi-

nucleated giant cells that are the hallmark of HIV infection of the brain (3, 21–23). Diffuse white matter signal abnormalities in HIV leukoencephalopathy are easily detected by MR imaging, and indicate an advanced stage of the disease. The MR findings in our study did not differ from those in other studies; signal intensity abnormalities in the white matter were present in all patients.

The initial treatment for ADC was zidovudine, a nucleoside analogue that inhibits viral reverse transcriptase. Several studies have shown a decline in the frequency and severity of ADC after zidovudine therapy (24–27). Partial resolution of MR signal abnormalities, followed by improved cognitive function, was reported in three patients with ADC treated with zidovudine (5). In another study, progression of encephalopathy associated with worsening atrophy on MR images and white matter lesions was observed in ADC patients undergoing zidovudine therapy (28). The effect of zidovudine on MR imaging signal changes has not been clearly defined; however, resistance to zidovudine has been reported in 30% to 80% of patients at various stages of the disease (8).

In 1996, the prognostic value of plasma viral load was recognized and a new therapeutic strategy was developed (8). This strategy relies on a combination of antiretroviral drugs with the goal of maximal suppression of viral replication. The most consistent antiretroviral effects have been seen with triple drug combinations, consisting of two NRTIs plus one protease inhibitor or two NRTIs plus NNRTI. There has been strong advice against the use of mono- or dual-nucleoside therapy because it promotes the development of viral resistance. On the other hand, for pharmacokinetic reasons, antiretroviral activity may be less efficient in the CNS than, for example, in plasma or lymph nodes. The CNS could act as a sanctuary for HIV and could therefore jeopardize the success of antiretroviral therapy in the long run.

Protease inhibitors are thought to penetrate poorly into the CNS, at least on the basis of CSF studies. Within this class, indinavir shows a somewhat better penetration (29). NNRTIs, such as nevirapine, and NRTIs, such as zidovudine, d4T, or 3TC, display much better CSF:plasma concentration ratios; however, CSF concentrations may not necessarily be representative of CNS concentrations. This is in accordance with the results of a recently published study in 16 AIDS patients with severe dementia in whom a strong relationship was shown between the use of protease inhibitors and improvement in cognitive function and in the extent of abnormalities observed on MR images (14). Follow-up MR images showed stabilization of encephalopathy in four of nine patients taking a protease inhibitor, and nearly complete regression in another four patients; only one patient had a slight progression of white matter disease. In that study, neuroimaging findings corresponded well with clinical improvement.

Contrary to that first published report on MR imaging findings in ADC patients receiving antiretroviral therapy including protease inhibitors, the first follow-up MR examinations in our study showed a progression of white matter signal intensity abnormalities in all patients. The drug regimen in our study also included one protease inhibitor. It is interesting that our patients were improving clinically and immunologically at that time. The first follow-up MR examinations in a study by Filippi et al (14) were performed 3 to 12 months (mean, 5 months) after the beginning of therapy. In our study, the first follow-up MR examinations were obtained at intervals of 1.5 to 9 months (mean, 6 months). Stabilization or regression of the white matter MR signal abnormalities was observed on subsequent images (mean, 11 and 20 months) in our patients, followed by further improvement in immune function.

The drug regimens in these two studies were also different. A triple combination therapy is now the mainstay of treatment for ADC (30). In our patients, quadruple therapy was initiated after ADC was diagnosed that consisted of nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, and one protease inhibitor. The quadruple antiretroviral therapy is not widely used, and its effects have not been clearly demonstrated.

Another difference between the studies is the fact that all patients in the study by Filippi et al (14) had undergone prior antiretroviral therapy and had received nucleoside analogues before taking a protease inhibitor. Although prior prolonged drug exposure is known to be one of the predictors of therapy failure with protease inhibitors, it seems that the efficacy of the antiretroviral therapy was not impaired in their study. In our group, three patients had no prior treatment but one patient had been treated. The discrepancies between our study and that of Filippi et al (14) could possibly reflect differences in the timing of the combination therapy, in the severity of the disease at baseline, and in the immune system response of the patients.

An initial increase of CD4+ T-lymphocytes, which was present in all our patients, is a result of redistribution from the lymph nodes rather than real recovery of the T-lymphocyte cells. Reduction in plasma HIV RNA followed by a further increase in the CD4+ count appears to be a better predictor of the efficacy of HAART. The progression of abnormalities on MR images on the first follow-up study should not be mistaken for therapy failure. It seems that it takes some time after the start of HAART in ADC patients for MR abnormalities to diminish or stabilize. The results of recent neuropathologic studies suggest that white matter abnormalities in ADC reflect a breakdown of the blood-brain barrier and increases in water content, which explains the reversible nature of the abnormalities. The antiviral effect of protease inhibitors, which were part of our drug regimen, is based on inhibition of HIV protease enzyme, resulting in the production of im-

mature noninfectious virions and subsequent interruption of viral spread. Neurotoxicity by HIV proteins and factors secreted by HIV-infected cells is lessened. The production of cytokines and other metabolic substances in the brain is not triggered by an immune response to viral load. The simultaneous reduction in the levels of viral factors at times preceding clinical improvement, provides compelling evidence that dementia is a metabolic encephalopathy fueled by HIV replication (31). Some other observations could also be important in understanding the discrepancies between the evolution of MR imaging findings, cognitive function, and immune status in ADC patients under HAART: 1) HIV-induced brain injury is probably a result of indirect mechanisms and production of diffusible factors, and the evolution of cognitive impairment may result from metabolic rather than structural injury, and 2) the pathogenetic relationship between cortical damage in ADC and clinical symptoms and viral loads is not clarified yet. The progression of atrophy in our patients under HAART seems not to correspond with improvement in immunologic status, in that, despite potent antiretroviral therapy, the neuronal damage appears to progress without clinical manifestation.

Although the characteristics of patients with ADC who respond to potent antiretroviral regimens should be elucidated further, the results of published studies as well as those in our series suggest that neurologic dysfunction and neuroimaging findings can improve, indicating that the disease may be at least partly reversible (14, 27, 32, 33). Ideally, therapy for HIV infection should be initiated before irreversible immunologic damage has occurred. There are unresolved questions concerning antiretroviral therapy. Examples of combinations in current use or under investigation are numerous. Constructing a potent combination from among the three current classes of drugs—nRTIs, NNRTIs, and protease inhibitors—requires a thorough knowledge of their mechanism of action, adverse effects, and potential drug interactions. Adequate interpretation of therapy response is an important part of the clinical management of AIDS patients with HIV dementia. It is crucial to include neuropsychological, neuroimmunologic, and virologic measurements, as well as neuroradiologic studies. The results of neuropsychological testing are not disease-specific and should always be interpreted in the context of the clinical neurologic evaluation. Currently, CD4+ count and determination of plasma HIV-1 RNA are used to monitor drug efficacy (34). The role of viral load determination in CSF should be evaluated further. The role of neuroimaging is evident, and the evolution of MR imaging findings should be established with larger series.

The results of the present study suggest that MR imaging may help in the clinical management of patients with ADC who are receiving potent antiretroviral therapy; however, neuroradiologists and clinicians should know that progression of signal intensity abnormalities on MR images on a first follow-up study does not necessarily imply therapeutic failure. Further work is needed to define the relationship between the long-term effects of therapy documented by neuropsychological and immunologic tests and the evolution of findings observed on follow-up MR images.

Conclusion

Although the patient sample in our study was small, the results suggest that MR imaging can be used to characterize changes due to HAART in AIDS patients with ADC. Combination drug therapy in patients with ADC may result in stabilization or even regression of signal intensity abnormalities observed on MR images. Larger series will be needed to confirm whether HAART can stabilize or even reverse HIV encephalopathy and to assess the rate of long-term effectiveness. Neuroradiologists should be aware of discrepancies in the evolution of MR imaging findings and immune function, particularly on first follow-up studies, which do not necessarily represent therapeutic failure. In addition, the role of MR imaging in monitoring therapeutic response should be clarified further.

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