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CT, MR, and Pathology in HIV Encephalitis and Meningitis

M. Judith Donovan Post¹ Larry G. Tate^{2,3} Robert M. Quencer¹ George T. Hensley^{2,3} Joseph R. Berger⁴ William A. Sheremata⁴ Gerd Maul⁵

The value and limitations of CT and MR in human immunodeficiency virus (HIV) infection of the brain was determined by a retrospective analysis of the CT scans (22) and MR images (7) in 22 patients with pathologically proved HIV encephalitis (21) or meningitis (1). Our clinical-radiologic-pathologic correlation suggested that, especially in the early stages of the disease, CT and MR were relatively insensitive in detecting the primary changes of HIV encephalitis. The multiple bilateral diffuse microscopic glial nodules with multinucleated giant cells of HIV found at autopsy in both gray and white matter were usually not directly visualized by either CT or MR. Secondary, nonspecific changes, however, were seen. These included cortical atrophy, found in virtually all patients with HIV encephalitis, and HIV-induced foci of demyelination found in the minority of cases. On CT the latter were seen in the white matter as nonenhancing, nonmass-producing areas of low density; on MR they were seen as frequently progressive high-intensity signal abnormalities on T2-weighted images, usually in the periventricular white matter and centrum semiovale. MR was more sensitive in detecting these demyelinative lesions than was CT. The clinical diagnosis of HIV encephalitis usually antedated the radiographic diagnosis. In HIV meningitis, contrast CT was more definitive than MR, showing striking enhancement of the subarachnoid spaces, although MR was more sensitive in detecting the secondary parenchymal changes.

Recently, the causative agent of AIDS, the human immunodeficiency virus (HIV), has been identified in the brains of AIDS patients, mainly in multinucleated giant cells or macrophages [1–5]. A clinical and pathologic correlation has been established between HIV infection of the brain and a progressive dementing encephalopathy that is commonly seen in AIDS patients [1–4, 6–14]. HIV has also been identified as a cause of acute and chronic meningitis [15–17]. Since the radiologic appearance of intracranial HIV infection has not been established, we reviewed the MR images and CT scans in 22 patients with pathologically proved HIV encephalitis or meningitis to determine the radiologic findings that characterize the disease and to compare the sensitivity of these imaging studies.

Materials and Methods

Twenty-two patients were identified who had either autopsy-proved HIV encephalitis (21) or culture-proved HIV meningitis (1). A correlation was then made retrospectively of the clinical, radiologic, and pathologic material.

In 20 patients, the autopsy diagnosis of HIV encephalitis was based on the finding of focal inflammation dominated by microglial nodules containing multinucleated giant cells (Fig. 1), as described previously in the literature [2]. These lesions were identified on routine microscopic examination with hematoxylin and eosin (H and E) stained slides. In one patient, the diagnosis was based on in situ hybridization of HIV in choroid plexus cells and by the electron microscopic identification of particles characteristic of HIV in the white matter but without evidence of budding virus. The diagnosis of HIV meningitis was made from the CSF, which was HIV-positive by Western Blot analysis and was also culture-positive; there was also evidence for intrablood-brain-barrier HIV-specific IgG synthesis. All but one patient had a

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¹ Department of Radiology, Section of Neuroradiology, University of Miami School of Medicine, P. O. Box 016960, Miami, FL 33101. Address reprint requests to M. Judith Donovan Post, R-109.

² Department of Pathology, University of Miami School of Medicine, Miami, FL 33101.

³ Department of Pathology, Broward Medical Examiners Division, Ft. Lauderdale, FL 33312.

⁴ Department of Neurology, University of Miami School of Medicine, Miami, FL 33101.

⁵ Wistar Institute, Philadelphia, PA 19104.

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Fig. 1.—HIV encephalitis—microscopic diagnosis. Slide of cerebral cortex (H and E ×90) shows microglial nodule (*long arrows*) with syncytial multinucleated giant cells (*short arrow*), findings characteristic of HIV encephalitis in 40-year-old IV drug abuser and homosexual with HIV-positive serology and AIDS syndrome and with 9-month history of progressive encephalopathy.

positive serum antibody test for HIV, and all but one patient had the AIDS syndrome as judged by clinical history and biopsy using criteria established by the Centers for Disease Control.

CT-enhanced studies were done in 17 patients, usually with a single-dose technique, but occasionally (in four) with a double-dose delayed technique [18]. MR studies were obtained in seven patients on mid- (0.5 T) and/or high-field-strength (1.5 T) magnets, and all patients were examined with spin-echo technique with both T1- and T2-weighted imaging.

Results

Clinical Data

The 22 patients were all men, ranging in age from 25 to 70 years (median, 36.5 years). Risk factors included (1) homosexuality, 15; (2) IV drug abuse, 4; (3) homosexuality and IV drug abuse, 1; (4) Haitian, 1; and (5) unknown, 1. Patients came to medical attention between 1983 and 1987, with the majority (15) seen in 1986. Twenty-one patients are dead and the one with meningitis is lost to follow-up.

Fourteen patients had a progressive encephalopathy occurring 1–12 months before death and characterized by a progressive alteration of mental status, confusion, slowness of thought process and speech, poor concentration, and memory loss. Dementia and inability to care for self were prominent features of the disease. In the remaining eight patients the clinical picture consisted of (1) meningeal symptoms and signs, 1; (2) seizures, 2; (3) lethargy for less than 2 weeks before death, 2; and (4) no intracranial symptoms, 3.

There was an excellent correlation between neurologic symptoms and pathologic findings in that in patients who were markedly encephalopathic there was usually severe HIV infection found at autopsy, even in those patients whose CT scans and MR images showed no parenchymal abnormalities.

Imaging Studies

All 22 patients were evaluated by CT at least once; 12 patients had serial examinations. Plain and contrast-enhanced scans were done in 16 patients. Five patients had only a noncontrast scan, and one patient had only a contrast study. MR scans were obtained in seven patients, three of whom had serial studies. The time between the final CT or MR study and the date of death in the autopsied patients ranged from 0-21 days in 10 patients, 1-4 months in eight, and 4-9 months in three.

Review of the CT scans revealed that atrophy was the most common CT finding. Cortical atrophy was seen in 20 of the 21 patients with HIV encephalitis (Fig. 2) and was mild in 12, moderate in seven, and marked in one. In those patients with serial scans the atrophy increased over a 3-6-month period. Ventricular dilatation on an ex vacuo basis was seen in 13 of 21 patients with HIV encephalitis, and was mild in eight and moderate in five. Of those patients whose ventricles were moderately dilated, four had evidence of deep white matter lesions. The second most common CT finding, seen in seven patients, was low-density parenchymal lesions that had no mass effect. These low-density areas were all located supratentorially and were found in the white matter in six patients (periventricular, six of six; centrum semiovale, five of six; internal capsule, one of six) and in the cortical gray matter in one patient. These hypodense lesions were subtle in three, being evident in one only on the follow-up study, and sizable and/or diffuse in four, seen only on the 3-7-month follow-up studies (Fig. 3). On final CT scans these parenchymal lesions were bilateral and symmetrical in five and unilateral in two. Contrast enhancement definitely related to HIV was seen only in the patient with HIV meningitis (Fig. 4).

MR images demonstrated cortical atrophy in six of the seven imaged patients, and was mild in three, moderate in two, and marked in one. Ventriculomegaly was seen in five patients, and was mild in three and moderate in two. Parenchymal lesions, identified as high-intensity signal abnormalities without mass effect on the T2-weighted spin-echo images were seen in five patients (Figs. 5 and 6). The other two patients had no parenchymal abnormalities despite the fact that they were imaged within 12-21 days of death and were encephalopathic. Of the five patients with parenchymal findings, two had subtle or mild lesions while three had striking abnormalities, which in one patient became worse on followup studies and in two patients were apparent only on the sequential examinations. Parenchymal findings in one of these five patients, however, were predominantly due to infarction caused by coexistent malignant angioendotheliomatosis and in another may have been related to infarction from meningitis. In the remaining three patients, the main areas of involvement were the periventricular white matter and centrum semiovale, with minor involvement in one patient of the internal capsule, cerebral peduncle, basal ganglia, and thalamus. Lesions ranged from small, scattered, and unilateral to sizable, bilateral, and confluent. Subtle meningeal abnormalities were detected only in the patient with HIV meningitis (Fig. 4).

Comparison of the CT and MR studies revealed that in two

Fig. 2.—HIV encephalitis—atrophy.

A and B, Initial plain (A) and double-dose delayed (not shown) CT scans were negative in this 25-year-old IV drug abuser with AIDS syndrome, HIV-positive serology, fever, and encephalopathy. Plain (B) and contrast CT 7 weeks later, after marked worsening of neurologic symptoms with lethargy and obtundation, demonstrated now diffuse cortical atrophy and ventriculomegaly and no parenchymal lesions. Autopsy, however, shortly thereafter revealed not only cortical atrophy but also considerable parenchymal changes with microglial nodules with syncytial multinucleated giant cells, severe in the central white matter, basal ganglia, and midbrain; moderate in the thalamus and ependymal cells; and mild in the corpus callosum and centrum semiovale. Demyelinating lesions in the cerebral peduncle and basal ganglia were also seen.



Fig. 3.—HIV encephalitis—focal and diffuse parenchymal abnormalities.

A, Initial contrast CT scan in 34-year-old homosexual man with HIV-positive serology and AIDS syndrome and a 2-month history of confusion, disorientation, and fever showed mild cortical atrophy and focal right frontal white matter low-density lesion (*arrow*), the biopsy of which was nondiagnostic, showing only necrotic tissue.

B, Contrast CT scan nearly 7 months later when the patient was encephalopathic showed an increase in cortical atrophy and ventricular size and marked progression of white matter changes in periventricular area and centrum semiovale (arrows). Autopsy revealed HIV encephalitis in cerebral cortex and centrum semiovale, diffuse demyelination, and cortical atrophy.



patients CT and MR were equivalent, since they both showed only cortical atrophy. In four patients MR was superior, since it demonstrated parenchymal disease when the initial CT was negative and/or showed more extensive disease when the CT scans were positive. MR was more sensitive than CT in detecting demyelinative lesions. In one patient CT was superior, since it showed diffuse meningeal disease to better advantage than did MR.

Pathologic Data

Coexistent disease was found in 11 patients (Table 1) and interfered with autopsy grading of the severity of HIV encephalitis in four. In the other 17 autopsied patients HIV encephalitic changes were graded as mild in three and ranged from mild to moderate in six, mild to severe in one, moderate to severe in three, and severe in four. The majority of HIV lesions were not seen on gross examination of the brain. Characteristically, they were of microscopic size and often of a diffuse nature. No large, focal, mass-producing lesions attributable to HIV were seen in any patient. Cortical atrophy, found in 20 patients, was thought to be related to HIV in all 20, although augmented by those coexistent infections that were severe.

The sites of HIV involvement and their occurrence in the patients with HIV encephalitis who could be graded are summarized in Table 2. The cerebrum was most commonly involved, followed by the brainstem, midbrain, and cerebellum. Only one patient did not have involvement of the cerebral



Fig. 4.—HIV meningitis.

A, Double-dose delayed CT scan in 31-year-old homosexual man with a history of chronic meningitis and HIV-positive serology demonstrated marked enhancement of intracranial subarachnoid cisterns (arrows) both infra- and supratentorially and subtle, small parenchymal low-density lesions (not shown). B and C, corresponding T2-weighted MR images (2000/60, 1.5 T) revealed less striking and less extensive abnormalities related to meningeal spaces, consisting of high-intensity signals mainly in area of left sylvian fissure (arrows in B) but more obvious parenchymal abnormalities (arrows in C). Cultures for bacteria, fungi, AFB, adenovirus, herpetic virus, and enteric viruses were negative, but CSF cultures were positive for HIV.



Fig. 5.—HIV encephalitis—parenchymal abnormalities.

A-C, 32-year-old homosexual male with AIDS syndrome and HIV-positive serology with progressive encephalopathy. Multiple CT scans (A) and T2weighted MR images (B and C) showed development of white matter lesions (*arrows*) around ventricles and in centrum semiovale without mass effect and with ventricular dilatation and cortical atrophy. Autopsy revealed extensive changes related to HIV in both cerebral gray and white matter. Severe demyelinative lesions were seen in particular in the centrum semiovale and cerebral peduncle.

hemispheres. The other 16 patients were found to have microglial nodules with multinucleated giant cells at multiple locations in both cerebral hemispheres. The frontal lobe was specifically involved in eight of these patients, the temporal lobe in eight, the occpitial lobe in two, and the insular cortex in two. Gray and white matter were affected both supratentorially and infratentorially. In eight patients microglial nodules with multinucleated giant cells in the white matter were ac-



Fig. 6.—HIV encephalitis—progression of parenchymal disease.

A, Initial plain CT scan (A) and MR image (not shown) demonstrated cortical atrophy and ventriculomegaly in a patient with HIV-positive serology and seizures, altered mental status, and bizarre behavior.

B, Second MR image (2000/80, 0.5 T) 1 month later revealed small parenchymal lesions in right periventricular area and left occipital lobe (arrows).

C and D, When patient became markedly encephalopathic 5 months later, a plain CT scan showed periventricular low-density white matter lesion (arrows in C) extending into centrum semiovale (arrows in D) and increasing atrophy.

E, Corresponding MR image (2000/80, 0.5 T) demonstrated not only the left occipital but also other lesions not seen on CT, such as those in the periventricular regions (arrows). A leukoencephalopathy secondary to HIV was found at autopsy that appeared microscopically more extensive than was shown on CT or MR.

companied by demyelinative lesions, some of which were grossly obvious. Four of these patients had large demyelinative lesions (which in three were also diffuse), one had a moderate-sized lesion, and three had small lesions. Inflammatory changes were mild. Astrocytosis was seen in five patients.

Comparison of CT and MR findings with pathologic material revealed a good correlation with respect to cortical atrophy

and to demyelinative white matter lesions. Five of the six patients with hypodense white matter lesions on CT and all three patients with white matter changes on MR had sizable demyelinative lesions at autopsy. In the two patients whose MR studies showed no parenchymal abnormalities, no demyelinative lesions were found at autopsy in one and only a tiny focus of demyelination was seen in the other. There were many lesions, however, that both CT and MR failed to detect.

TABLE 1: Coexistent CNS Disease in 21 Autopsied Patients with HIV Encephalitis

Finding	No. of Patients
Meningovascular syphilis	3
Cytomegalic inclusion virus infection (CMV)	3
Toxoplasma encephalitis	2
Cryptococcal infection	1
Progressive multifocal leukoencephalopathy (PML)	1
Malignant angioendotheliomatosis	1

TABLE 2: Location of HIV Infection at Autopsy in 17 Patients^a

Site of Involvement	No. of Patients
Cerebral cortical gray matter	16
Cerebral subcortical white matter	15
Centrum semiovale	11
Periventricular white matter	9
Corpus callosum	7
Internal capsule	7
Basal ganglia	11
Thalamus	8
Midbrain	13
Brainstem	14
Cerebellum	9

^a Refers to the finding of focal inflammation dominated by microglial nodules containing multinucleated giant cells.

HIV lesions in the brainstem, cerebellum, and midbrain were particularly prone to being missed. In fact, no lesions were demonstrated in the posterior fossa in any patient on either imaging technique despite brainstem and cerebellar involvement seen at autopsy in 14 and nine patients, respectively. Of 13 patients with midbrain involvement at autopsy, only one had a radiographic abnormality. Supratentorially, both gray and white matter lesions were also frequently missed. For example, with regard to the cortical gray matter, basal ganglia, and thalamus, CT or MR abnormalities were seen in only one patient in each of these locations despite pathologic involvement of these areas in 16, 11, and eight patients, respectively. White matter lesions unassociated with foci of demyelination were also not usually detected. As for those cases in which CT and MR were positive for parenchymal lesions, the extent of the disease was usually underestimated by both techniques.

Discussion

In clinical series, 31–60% of AIDS patients have been reported to develop neurologic complications [15, 19, 20]. Autopsy series, however, have indicated that these figures underestimate the true frequency of neurologic disease in AIDS, since positive findings at autopsy have been reported as ranging between 73–87% [6, 19, 21]. Despite this high frequency of neuropathologic abnormalities, a recognized opportunistic infection or neoplasm has not often been identified

as the underlying cause [2, 20, 22]. In clinical studies, too, a specific cause of CNS symptomatology in AIDS patients has not often been delineated. Individuals with unexplained clinical courses have been those with a subacute encephalitis and dementia; these constitute about one-third of AIDS patients [2, 16, 20]. Such individuals have developed personality changes, confusion, memory loss, and dementia, often culminating in the course of weeks to months in severe global cognitive impairment [8]. Their autopsy examinations have revealed scattered microglial nodules with multinucleated giant cells, cerebral atrophy, foci of demyelination, and a paucity of inflammatory cells [8, 20, 22].

Unexplained cases of subacute encephalitis, meningitis, myelopathy, and neuropathy [16] in a significant portion of the AIDS population has led to the suggestion that HIV, the causative agent of AIDS, not only is lymphotropic but also neurotropic. That HIV is present and expressing itself in the brain comes from the work of Shaw et al. [8], who found HIV DNA and RNA sequences in the brains of patients with AIDS encephalopathy. Ho et al. [16]-through virus-isolation studies of HIV in the CSF, brain, spinal cord, and peripheral nerve in AIDS patients with neurologic symptoms-demonstrated that HIV plays an important role in the neurologic disease that accompanies AIDS or ARC. Other researchers have shown that HIV may infect neurologic tissue early, as evidenced by the intrablood-brain-barrier synthesis of HIV-specific antibody [7, 23-25]. However, HIV-specific antigen may correlate better with neurologic dysfunction than does HIV-specific antibody in the CSF [26].

The major cell type in the brain that might be the target for HIV infection and the site of HIV replication, as well as the cause of progressive encephalopathy of AIDS, has been identified by various techniques as the mononucleated and multinucleated macrophages, or giant cells [1-5]. Multinucleated giant cells containing HIV DNA and RNA have been found scattered in both white and gray matter, near blood vessels, and in areas of demyelination [1, 2, 4, 5]. The presence of HIV antigen in these cells appears to correlate with the severity of the subacute encephalitis [3]. While astrocytes, oligodendroglia, and, rarely, neurons have also occasionally been infected by HIV, the multinucleated giant cells appear to be the main target of HIV [1, 3-5]. A possible source of these infected brain cells has been postulated as being the peripheral blood monocytes, which when infected may cross the blood barrier and differentiate into giant cells [2]. The infected giant cells might then cause white matter damage and impaired neural transmission by secreting toxic factors or by evoking a delayed-type hypersensitivity response as a reaction to HIV antigen [2, 3].

The radiologic evaluation of AIDS patients with subacute encephalopathy has generally not been rewarding, other than to exclude other neurologic diseases that may complicate AIDS [17]. The most commonly reported abnormality on CT has been cerebral atrophy, with white matter abnormalities infrequently observed [11, 19, 20, 26, 27]. More recently, however, diffuse white matter disease has been reported on MR in an HIV-seropositive patient with progressive dementia in whom CT was negative and in whom the HIV was cultured from the brain [4]. Other investigators have also suggested Our study indicates that both CT and MR are relatively insensitive, especially early on, in the detection of the microglial nodules with multinucleated giant cells that are the hallmark of HIV encephalitis. Despite widespread lesions seen at autopsy in our patients with encephalopathy, initial CT and MR usually missed or grossly underestimated the primary parenchymal abnormalities of this infection. We postulate that this insensitivity is due in part to the microscopic size of the lesions and their often diffuse, nonfocal, nonmass-producing nature, and in part to the fact that they elicit little edema. As opposed to many other AIDS-related lesions, such as toxoplasma encephalitis and lymphoma, the primary lesions of HIV encephalitis are not characteristically large and focal and do not evoke a severe inflammatory response.

The changes that CT and MR appeared to detect best were secondary ones; namely, cortical atrophy and demyelinative lesions. Cortical atrophy was a characteristic finding and was useful in indirectly suggesting HIV involvement of the cortex. Demyelinative lesions secondarily induced by HIV were also recognized radiographically, especially by MR, if they were not extremely small; but they often appeared to be late findings, since initially they could be absent or small, few in number, and unilateral, and only later progress over many months to large, bilateral, confluent areas. This experience leads us to believe that the leukoencephalopathy induced by HIV does not occur early in the disease but takes time to develop, indicating the need for time-interval MR studies. These secondary radiologic findings in HIV encephalitis are not specific. Nonenhancing, non-mass-producing foci of demyelination can be seen in progressive multifocal leukoencephalopathy (PML) and in cytomegalovirus (CMV) encephalitis, although PML favors the parietal and occipital lobes and is not as commonly seen in the frontal lobes as in HIV encephalitis. Infarcts may also be seen in AIDS patients and may occasionally simulate HIV encephalitis [17, 19, 20, 22, 29].

The need for a prospective study is evident from the limitations of our retrospective investigation because such a study would allow for a much closer radiologic-pathologic correlation. A prospective study would also allow for the routine acquisition of immunoperoxidase stains for identification of HIV antigen, and myelin sheath stains for the localization of foci of demyelination.

Based on the results of our study we recommend that in HIV-positive patients with encephalopathy, thin section, multiplanar MR be the initial screening examination. If findings atypical of HIV encephalitis are seen, such as focal mass lesions, contrast CT scans should be obtained to help diagnose those lesions that typically enhance in AIDS patients, such as toxoplasma encephalitis and lymphoma. If, on the other hand, the initial MR is negative, serial MR studies should be performed to look for cortical atrophy and white matter lesions that would make HIV encephalitis a likely diagnostic possibility. As for HIV-positive patients with meningeal symptoms, both a contrast CT and an MR are suggested, since the information they provide is complementary. When gado-linium is generally available, CT may not be necessary.

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