Microglial Nodular Encephalitis and Ventriculoencephalitis Due to Cytomegalovirus Infection in Patients with AIDS: Two Distinct Clinical Patterns

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In patients with AIDS, cerebral infection due to cytomegalovirus (CMV) results in two distinct neuropathological patterns: microglial nodular encephalitis (MGNE) and ventriculoencephalitis (VE). In order to identify clinical features to facilitate the differential diagnosis of these two forms of CMV encephalopathy in living patients, we retrospectively reviewed the clinical records of 18 patients with MGNE or VE diagnosed at autopsy. We identified the following clinical features as distinguishing the two encephalopathies: (1) MGNE manifests earlier than VE; (2) the onset of MGNE is acute, whereas the onset of VE is insidious; (3) the onset of MGNE is marked by confusion and delirium, which do not occur in VE; (4) VE is frequently associated with radiculopathy, which is absent in MGNE; and (5) VE is associated with more marked alterations in cerebrospinal fluid (high protein levels and pleocytosis). The early neurological manifestations of MGNE should prompt a search for systemic CMV infection, which may lead to earlier treatment.

Histopathologic Examination

Brain tissues were fixed in 10% buffered formalin and embedded in paraffin. Sections from the frontal, parietal, and temporal cortex, basal ganglia, cerebellum, and spinal cord and from each macroscopic lesion were stained with hematoxylin and eosin for histologic examination. Other stains, including periodic acid–Schiff, Ziehl-Neelsen, and Giemsa preparations, were used as required.

Immunohistochemistry was performed on 3-μm CNS sections previously dewaxed in xylene and rehydrated in graded ethanol. Slides for immunohistochemical detection of CMV and HIV were pretreated with type XIV protease (0.5 mg/mL) and microwave heating (2 × 5 minutes at 780 w). Three antibodies were used: mouse monoclonal antibody to CMV (Dako, Italy), rabbit polyclonal antibody to Toxoplasma gondii (Dako), and mouse anti-HIV core protein p24 (Dako). One hundred microliters of antibody (diluted 1:50 in bovine serum albumin 1%) was applied overnight at room temperature. The immunocomplex was detected by the double indirect immunoperoxidase technique with 3,3’-diaminobenzidine free base as chromogen.
Clinical Assessment

When the autopsy results were available, the clinical records of cases meeting study criteria were reviewed to extract the following: patients’ characteristics; onset symptoms; signs noted at neurological examination; MRI and CT findings; result of CSF examination (if spinal tap was performed); clinical stage of systemic HIV (per the Centers for Disease Control and Prevention [CDC] classification [6]); CD4 lymphocyte count; result of blood assay for CMV pp65 antigen; any nonneurological condition attributable to CMV; dose and duration of treatment with gancyclovir or foscarnet; and dose and duration of treatment with zidovudine.

All patients were examined by a specialist in infectious diseases. Those who developed visual disturbances were examined by an oculist experienced in AIDS treatment. One neurologist (M. P. G.), experienced in the neuro-AIDS field, examined all the patients with use of a standardized procedure [7] that assessed the cognitive state (spatial and temporal orientation, memory, ideation); cranial nerves; pyramidal system (overall muscle strength, stretch reflexes, plantar reflex); extrapyramidal system (rigidity, tremor(s), alternating finger and hand movements, postural reflexes); cerebellum (nystagmus, coordination, intentional tremor, ataxia); sensory aspects (pain sensitivity, graphesthesia); peripheral aspects (segmental muscle strength, radicular distribution of sensitivity, reflexes); and frontal release signs (snout reflexes, pal momentum reflex, grasp reflex). Each parameter was assigned a score of 0 (normal) or 1 (pathological).

Cerebral CT was routinely performed with and without contrast. In some cases T1 and T2-weighted MR images were obtained. The following were assessed on examination of CSF: cell count, glucose level, and protein concentration. In some cases, CMV DNA was assayed for by PCR [8].

Results

Pathological Examination

Of 744 neurologically symptomatic HIV patients presenting over the study period, autopsies were performed on 163. Of these, 34 presented with cerebral features characteristic of CMV infection, 16 of which were excluded because of HIV encephalopathy (2 cases), cerebral neoplasm (2 cases), or opportunistic cerebral pathology (12 cases). Of the 18 remaining cases, 7 were of MGNE and 11 were of VE. MGNE presented with microglial nodules formed by rod cells, few lymphocytes, and macrophages; no tissue damage was demonstrated around them. In all these cases, cells with cytological alterations attributable to CMV infection were observed in at least one microglial lesion. The spinal cord in these cases was histologically normal.

VE presented as necrotizing encephalitis limited to periventricular areas, with numerous cytomegalic cells in and around the lesion. The cervical region of the spinal cord was examined in 5 MGNE and 10 VE cases; it was found normal in all 5 MGNE and 5 VE cases. In the other five VE cases, tissue damage and cytomegalic cells were observed in the subpial region.

Monoclonal antibodies to CMV routinely stained nuclei and cytoplasm in cytomegalic cells and also in occasional morphologically normal cells. Immunostaining for HIV or T. gondii antigens was negative in all the cases selected.

General autopsy revealed extracerebral CMV infection in 9 patients (5 with MGNE and 4 with VE): adrenal infection in 4 MGNE and 3 VE patients, lung infection in 2 VE patients, digestive system involvement in 1 MGNE patient, and spleen involvement in 1 VE patient. In no cases were the eyes examined.

Patients’ Characteristics

The characteristics of the two groups of patients are shown in table 1. MGNE patients were younger than VE patients but not significantly so. Male drug users formed the majority of each group. At the onset of neurological symptoms, absolute CD4 lymphocyte counts were very low in both groups, with no significant difference between them. According to the CDC criteria [6], most patients with MGNE were at the pre-AIDS stage when they developed neurological symptoms.

By contrast, the majority of VE patients had full-blown AIDS and had CMV-related extraneurological signs and symptoms before manifesting cerebral CMV.

Extraneurological CMV Infection

All patients tested positive for the CMV pp65 antigen in blood during their neurological illness. Twelve patients had

<table>
<thead>
<tr>
<th>Field</th>
<th>MGNE (n = 7)</th>
<th>VE (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (SD)</td>
<td>32.43 (4.20)</td>
<td>36.36 (7.47)</td>
</tr>
<tr>
<td>Sex, M/F ratio</td>
<td>5/2</td>
<td>8/3</td>
</tr>
<tr>
<td>Risk factors: drug abuse/sexual contact</td>
<td>5/2</td>
<td>6/5</td>
</tr>
<tr>
<td>CD4 cell count, mean (SD)</td>
<td>20.71 (26.02)</td>
<td>11.36 (8.6)</td>
</tr>
<tr>
<td>CDC stage IVC2 (pre-AIDS)</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>CDC stage IVC1-IVD (AIDS)</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>AIDS-defining illness:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extraneurological CMV disease</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Mycobacteriosis</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Pneumocystis carinii pneumonia</td>
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<td>3</td>
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<tr>
<td>Esophageal candidiasis</td>
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<td>3</td>
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<tr>
<td>Kaposi’s sarcoma</td>
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<td>2</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
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</tr>
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</table>

NOTE. CDC = Centers for Disease Control and Prevention; CMV = cytomegalovirus; MGNE = microglial nodular encephalitis; VE = ventriculoencephalitis.
CMV retinitis, before neurological presentation (8 patients: 1 with MGNE, 7 with VE) or after (4 patients: 3 with MGNE, 1 with VE). Two MGNE patients with CMV retinitis also developed CMV pneumonia (one before and one after neurological onset).

### Clinical Features

**CNS.** Table 2 lists symptoms at neurological onset. In all MGNE patients, onset was characterized by acute confusion associated with delirium and psychomotor agitation. In addition, three patients had hallucinations, and in one patient the onset was also marked by a generalized seizure.

In contrast, the neurological onset of VE was insidious and usually characterized by the development of cognitive disturbances, such as mental slowness and memory deficits. Occasionally, headache, seizures, and ambulation difficulties marked the neurological onset. Four VE patients with cerebral CMV infection had no CNS symptoms; they were referred for neurological examination following the development of lower-limb paresthesia.

Table 3 summarizes results of the neurological examination, performed 0.67 months (SD, 0.82) after onset for MGNE patients and 2.36 months (SD, 2.15) after onset for VE patients. The only cranial nerve deficit observed was nystagmus.

**Peripheral nervous system.** Signs of lower-limb neuropathy were observed in four MGNE and five VE patients (table 3). By contrast, lumbosacral radiculopathy was observed in six VE patients only; it manifested as cauda equina syndrome in four and L5 radiculopathy in two. The spinal cord was examined histologically in five of these cases, yielding positive findings in three cauda equina cases and negative findings in a case of cauda equina syndrome and L5 radiculopathy.

**CSF.** Four MGNE and four VE patients underwent lumbar puncture at 11 weeks (SD, 11.75 weeks) and 18.75 weeks (SD, 30.32 weeks), respectively, following neurological onset. Total protein concentrations were 60.5 mg/dL (SD, 11.2 mg/dL) and 171.5 mg/dL (SD, 139 mg/dL), respectively, while the glucose levels were 40 mg/dL (SD, 8.68 mg/dL) and 35.25 mg/dL (SD, 8.22 mg/dL). Cells were absent in all MGNE and two VE patients; in the other two VE patients WBC counts were 50/mL and 10/mL (in both cases, 60% lymphocytes and 40% polymorphonuclear cells). PCR for CMV was performed in 1 MGNE and 1 VE patient (results were positive for the former and negative for the latter).

### Radiological Features

Patients underwent repeated cerebral CT, with and without contrast; in all cases it revealed superficial and deep supratentorial atrophy, frequently associated with subtentorial atrophy. Eight patients (two with MGNE and six with VE) underwent cerebral MRI (T$_1$- and T$_2$-weighted), and in all of them cerebral atrophy was observed. Discrete lesions of the cerebral parenchyma were not observed, either by CT or MRI. Three of the six VE patients with radiculopathy underwent lumbosacral MRI, which yielded normal findings.

### Course, Treatment, and Outcome

The acute confusion with delirium, restlessness, and agitation that developed in all MGNE patients at neurological onset regressed in a few days, either spontaneously (4 of 7) or following administration of sedatives (3 of 7). However, in all cases...
there were residual cognitive alterations (one or more of the following: cognitive slowing, memory deficit, or disorientation). Three MGNE patients underwent repeated neurological examinations 3.25 months (SD, 1.89 months) before death, but the signs of encephalopathy had not worsened. A second neurological examination was also performed on four VE patients 12.25 months (SD, 6.24 months) before death, and their course was relatively stable.

Fifteen patients received therapy for CMV infection during their neurological illness, mainly to control the extraneurological symptoms of the infection. Nine patients (1 with MGNE, 8 with VE) began treatment before neurological onset, and the remaining 6 (4 with MGNE, 2 with VE) began treatment after neurological onset. Seven patients (4 with MGNE, 2 with VE) were receiving therapy with zidovudine at neurological onset, which continued at a dosage of 507.14 mg/d (SD, 271.46 mg/d) for an average of 13 weeks (SD, 8.96 weeks), but in no case was neurological improvement noted.

The mean time between neurological onset and death was 4.71 months (SD, 3.25 months) for MGNE patients and 6.72 months (SD, 5.70 months) for VE patients. In all cases, death occurred following the development of nonneurological complications related to immunodeficiency.

**Discussion**

The cases in this study were selected on the basis of the autopsy finding of MGNE or VE due to CMV, in the context of HIV positivity. In life, all underwent neurological examination following the onset of neurological symptoms. Patients with any other cerebral pathology revealed at autopsy; psychiatric, metabolic, or other neurological conditions; or receiving psychotropic drugs were excluded. It is therefore reasonable to conclude that the neurological symptoms and signs in these patients were due to CMV encephalitis only. Comparison of the two groups revealed several important elements concerning the differential diagnosis of MGNE and VE in living patients with HIV-related CMV infection.

**Onset.** Neurological signs of CMV infection are usually late complications of HIV infection and present in association with extraneurological signs of CMV infection [3, 5, 9–13]. Our study confirms this but shows that MGNE is characterized clinically by a slightly earlier neurological onset than in less severely immunosuppressed patients. Neurological signs of MGNE usually appeared before the onset of other AIDS-defining illnesses and even before extraneurological CMV infection had become evident. By contrast, neurological signs of VE usually developed after other AIDS-defining illnesses and extraneurological CMV infection occurred.

**Clinical presentation.** In the patients shown to have MGNE, neurological onset was acute and characterized by confusion with delirium and, in three cases, hallucinations; in patients shown to have VE, however, neurological onset was insidious. Britton et al. [14] described a similarly acute onset in two MGNE patients, whose symptoms were “paranoia, hostility, delusions, and agitation.”

In the large series of MGNE patients described by Holland et al. [9], delirium was a recurrent disturbance, but—unlike in our series—it was noted in the late stages of the illness rather than at onset.

Neurological examination revealed no other characteristics for distinguishing MGNE from VE: pyramidal, extrapyramidal, cerebellar, and sensory functions were equally compromised in the two groups.

**Concomitant peripheral nerve syndromes.** Two CMV-related peripheral nerve syndromes are recognized in patients with AIDS: multifocal neuropathy [15] and radiculopathy, including subacute ascending lumbosacral polyradiculomyelopathy (PRAM), also known as cauda equina syndrome [12]. In the former syndrome, CMV is present in peripheral nerves [15]; in the latter, there is a direct root and spinal cord involvement [10, 12].

Our finding was that both forms of CMV encephalitis could be associated with peripheral neuropathy, but only VE was associated with radiculopathy; furthermore, VE was generally associated with PRAM. This agrees with the findings of several previous studies: Kalayjian et al. [4] reported a high incidence of CMV radiculitis in their population of VE patients, and several others have noted an association between VE and PRAM [10, 13, 16–18].

In this context we note the speculation of Eidelberg et al. [10] that radiculopathy probably arises because infected ependymal cells become detached and travel in the CSF to eventually implant caudally. This suggestion, later taken up by Mahieux et al. [17], would explain the clinical finding of radiculopathy and the histologic finding of spinal cord involvement in some VE cases: those in which CMV disseminated ependymally. It is not clear, however, why histologic involvement of the spinal cord was demonstrated only in some VE patients with clinical radiculopathy and why only some VE patients with histologic myelopathy presented with radiculopathy while alive. It is plausible, as indicated in a previous report [19], that patients with symptomatic lumbosacral roots but a histologically uninvolved cervical spinal cord may have had lower spinal cord involvement, but this was not assessed at autopsy.

**CSF abnormalities.** VE was associated with frequent CSF pleocytosis—which was absent in MGNE cases—and with higher CSF protein levels (171.5 mg/dL [SD, 139 mg/dL] vs. 60.50 mg/dL [SD, 11.2 mg/dL]). These differences are again probably related to the differing propagation modes of cerebral CMV infection in the two pathologies. CMV DNA was assayed for in only two patients, because when most cases were followed (1990–1996), PCR was not yet in routine use.

The lack of systematic follow-up for these patients is due to the nature of the study; performed retrospectively, its aim was to determine whether the clinical characteristics of the two autopsy-defined groups differed. Perhaps a prospective study involving inter alia MRI and CMV PCR would bring to light
further criteria for the differential diagnosis of MGNE and VE in living patients.

To conclude, MGNE should be suspected in HIV-positive, AIDS-free patients with acute-onset psychiatric disturbances who do not have signs of radiculopathy or major CSF alterations. By contrast, insidious onset of encephalopathy in an AIDS patient with signs of radiculopathy and pleiocytosis, an increased CSF protein level, and CMV DNA in the CSF should orient the diagnosis to VE and CSF dissemination of CMV.

Diagnosis of these conditions in life has therapeutic implications, particularly for patients with MGNE. Such patients are not suspect for CMV infection since other organs are not involved, but our study indicates they will develop systemically disseminated CMV infection. Therefore, early suspicion of MGNE could facilitate early recognition and treatment of the systemic disease, with considerable benefit to the patient.

The identification of clinical criteria for distinguishing the two pathological forms of CMV encephalitis also suggests the need for studies on larger groups of patients to identify possible differences in response to antiviral therapy.

References