

## NEUROCRITICAL CARE THROUGH HISTORY



# It was 40 Years Ago Today: AIDS and the Brain

Eelco F. M. Wijdicks\* 

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The year 1980 marks the first case of acquired immunodeficiency syndrome (AIDS). The year 1982 marks the first case of a brain lesion in AIDS describing progressive multifocal leukoencephalopathy (PML), which was followed by central nervous system (CNS) toxoplasmosis a year later. These were the first indications that patients with AIDS could succumb from acute, highly unusual brain infections. Although these viral and parasitic infections were rarely seen, they flourished in the severely compromised immune systems of patients with AIDS.

The first reporting in the Centers for Disease Control and Prevention (CDC) *Morbidity and Mortality Weekly Report* involved only five cases of AIDS. On that day, the CDC reported pneumocystis carinii pneumonia in previously healthy men and, later, a spike in cases of Kaposi sarcoma among gay men in New York. The CDC has since reported AIDS-related deaths of more than 32 million people worldwide since the start of the global pandemic—one of the worst pandemics in history, together with bubonic plague during the fourteenth century (estimated 50 million) and 1918 flu pandemic (100 million).

### The First Cases of CNS Involvement in AIDS

On December 2, 1982, the *New England Journal of Medicine* reported PML in a “male homosexual with T-cell immune deficiency” (Fig. 1). This case report in a 39-year-old man was notable for rapid clinical progression of the disorder. The diagnosis was achieved by biopsy of a cerebellar lesion, the patient’s prior history of syphilis, recent weight loss, and hepatosplenomegaly.

The neurological examination revealed findings not only pertaining to cerebellar dysfunction, including lateral gaze nystagmus, but also pertaining to brainstem injury, with diminished left-sided pinprick and hand sensation on the face and left arm. Both cerebellar and brainstem findings worsened, and corticospinal tract dysfunction was also noted.

The original computed tomography scan featured “a large lucent lesion” in the cerebellum without edema. Biopsy of the lesion showed microglial cell response and giant astrocytes, with electron microscopy confirming intracellular viral particles and filaments typical of the papovavirus virion. Despite treatment with intravenous vidarabine, the patient died of respiratory failure 2 months after the initial presentation. The authors noted that although infection with JC virus is common, it is rarely symptomatic and destructive, even when it affects patients in an immunocompromised state (viral DNA is detected in 20–30% of immunologically normal adults’ urine [1]). This first presentation marked the “opening salvo” of many CNS complications, which included encephalitis from cytomegaly virus infection or from toxoplasma gondii. Other neurological conditions seen were meningitis caused by *Cryptococcus neoformans* and *Aspergillus fumigatus*.

A second landmark article by Whelan et al. [2] (Fig. 2) observed 19 patients with CNS involvement in the setting of “homosexuality, intravenous drug abuse” ranging in age from 26 to 56 (but only three patients were over the age of 40). Fourteen of these 19 patients progressed to Kaposi syndrome and pulmonary and gastrointestinal infections, which included pneumocystis carinii, cytomegaly, and parasitic and fungal infection. The lesions noted were intraparenchymal or meningeal *Toxoplasma gondii*, an infection previously seen in only immunocompromised hosts. Nine patients were diagnosed with cryptococcal meningitis, as demonstrated

\*Correspondence: wijd@mayo.edu  
Division of Neurocritical Care and Hospital Neurology, Mayo Clinic, 200  
First Street SW, Rochester, MN 55905, USA

**PROGRESSIVE MULTIFOCAL  
LEUKOENCEPHALOPATHY IN A MALE  
HOMOSEXUAL WITH T-CELL IMMUNE  
DEFICIENCY**

JAMES R. MILLER, M.D.,  
ROBERT E. BARRETT, M.D.,  
CAROLYN B. BRITTON, M.D.,  
MICHAEL L. TAPPER, M.D.,  
GERALD S. BAHR, M.D.,  
PETER J. BRUNO, M.D.,  
MERLIN D. MARQUARDT, M.D.,  
ARTHUR P. HAYS, M.D.,  
JAMES G. MCMURTRY III, M.D.,  
JACK B. WEISSMAN, M.D.,  
AND MICHAEL S. BRUNO, M.D.

AN acquired immune deficiency in male homosexuals that is manifested by infection with one or more opportunistic microorganisms has recently been recognized. These agents have included cytomegalovirus, *Toxoplasma gondii*, *Pneumocystis carinii*, *Candida albicans*, *Mycobacterium avium-intracellulare*, and *Cryptococcus neoformans*.<sup>1-4</sup> A prolonged clinical course with an otherwise self-limited infection, such as herpes simplex infection, has also been described,<sup>3</sup> and a remarkable incidence of Kaposi's sarcoma has been reported.<sup>1-5</sup>

In this milieu, the occurrence of progressive multifocal leukoencephalopathy (PML) might be expected. We present the case of a male homosexual with a T-cell immune deficiency, in whom PML was suspected because of a progressive disorder of the brain stem and cerebellum, as well as a lucent cerebellar lesion demonstrated by computerized tomography (CT). The diagnosis was confirmed by biopsy of the cerebellar lesion.

The white-cell count was  $3.3 \times 10^9$ , with 22 per cent polymorphonuclear leukocytes, 13 per cent band neutrophils, 51 per cent lymphocytes (mostly atypical), 12 per cent monocytes, and 2 per cent eosinophils. Blood chemistry and electrolyte levels were normal except that the alanine aminotransferase was 57 U ( $0.645 \mu\text{mol} \cdot \text{sec}^{-1} \cdot \text{liter}^{-1}$ ). Serum protein electrophoresis was normal. Immunoglobulins were present at the following levels: IgG, 1450 mg per deciliter (normal, 660 to 1274); IgM, 335 mg per deciliter (normal, 75 to 270); and IgD, 1.7 mg per deciliter (normal, undetectable). Skin tests with purified protein derivative, trichophyton, mumps, and candida antigens did not evoke responses. The proportion of T cells was decreased (57 per cent; normal, 60 to 80), and that of B cells was increased (21 per cent; normal, 8 to 12) in peripheral-blood leukocytes. The ratio of OKT4 to OKT8 cells was 0.46 (control, 1.95).

Serologic studies demonstrated previous infection but no evidence of active infection from toxoplasma, cytomegalovirus, Epstein-Barr virus, or hepatitis B virus. A serologic test for syphilis was negative. The hemagglutination inhibition titer to JC virus was 1:64, which was consistent with previous infection.

Repeated cultures for infectious agents, including blood and urine studies for cytomegalovirus, were negative.

Cerebrospinal-fluid examination, which included bacterial, fungal, viral, and cytologic studies, gave normal results except for a protein level of 57 mg per deciliter (0.57 g per liter). A repeat examination performed two weeks later showed a negative Venereal Disease Research Laboratory test and Sabin-Feldman dye test, but oligoclonal bands were present that were atypical for demyelinating diseases or acute central-nervous-system infections. IgG made up 11.4 per cent of the total cerebrospinal-fluid protein. An electroencephalogram was normal, but a CT scan of the brain showed an area of decreased density in the left cerebellar hemisphere without contrast enhancement or mass effect (Fig. 1).

Left-sided cerebellar and brain-stem signs increased, and the patient became unable to walk. Corticospinal-tract dysfunction was

**Fig. 1** Title page on progressive multifocal leukoencephalopathy in acquired immunodeficiency syndrome. (Reprinted with permission from Miller JR, Barrett RE, Britton CB et al. Progressive multifocal leukoencephalopathy in a male homosexual with T-cell immune deficiency. N Engl J Med. 1982;307(23):1436-8.)

by elevated cryptococcal cerebrospinal fluid (CSF) antigen India ink stains. Patients rapidly became critically ill with seizures and decline in their level of consciousness with intermittent focal findings [2]. The multiple bilateral lesions of different sizes and significant enhancement are shown in Fig. 3. The article also noted a poor inflammatory response, with often acellular CSF in patients with cryptococcal infection, often with unusually low CSF white blood cell counts, which ranged from 0 to 10 lymphocytes. Mortality in this group was high, but there was also clinical improvement and no recurrence several months later after adequate treatment with anti-toxoplasma therapy.

A third confirmatory article was by Levy et al. [3], from the Department of Neurological Surgery at the University of California, San Francisco. The authors presented nine patients evaluated between April 1979 and July 1983. At the time, approximately 10% of the CDC's 2,000 reported cases of AIDS had CNS involvement, which now extended also to primary lymphoma, but again most

were *Toxoplasma gondii* infections. The outcome was much worse, with eight of the nine described patients dying of unknown CNS disease [3].

### A Painful Legacy

All these findings of rapid neurocritical illness as a result of AIDS therefore suggest the serious impact of AIDS on the CNS. Historically, this was an unusual and unpredicted early consequence of a rapidly emerging pandemic. Within the next few years, the CNS became the second-most affected system in patients with AIDS. Many neurologists at the time pointed out that the neurologic signs were subtle in AIDS but became apparent because of hospitalization [4]. CNS involvement added to the suffering of patients and also heightened the fear of neurosurgical teams about the risks of infection from operating on patients infected with AIDS.

Looking back over 40 years, we find little to celebrate. This anniversary reminds us that even after introduction of highly active antiretroviral drugs, morbidity and

## NEURORADIOLOGY

Margaret Anne Whelan, M.D.  
 Irvin I. Kricheff, M.D.  
 Michael Handler, M.D.  
 Victor Ho, M.D.  
 Kenneth Crystal, M.D.  
 Govindan Gopinathan, M.D.  
 Linda Laubenstein, M.D.

## Acquired Immunodeficiency Syndrome: Cerebral Computed Tomographic Manifestations<sup>1</sup>

CT examination of the central nervous system was performed in 19 patients with acquired immunodeficiency syndrome (AIDS). Eighteen patients were homosexuals, and five drug abusers. Parenchymal and meningeal inflammations were seen in patients with intracranial manifestations of the disease. The most common demonstrable lesion in the parenchyma was toxoplasmosis, which produced ring enhancement, solid enhancement, and nonenhancing focal edema. The most common meningeal inflammation was cryptococcosis, which was diagnosed by examination of the cerebrospinal fluid and did not show specific CT changes. It is concluded that toxoplasmosis and cryptococcosis should be the first diagnostic consideration in patients with neurologic findings who have a history of homosexuality and/or intravenous drug abuse and previous unusual infections or anergy. A delayed contrast scan, single or double dose, appears to be the most accurate method of outlining the total extent of disease thereby helping to locate the best biopsy site for pretreatment diagnosis. Empirical institution of toxoplasmosis therapy is recommended in those cases in which CT findings are consistent with toxoplasmosis and the biopsy shows only nonspecific encephalitis. A biopsy of every parenchymal lesion is not considered necessary.

**A**N INCREASING number of reports on acquired immunodeficiency syndrome (AIDS) have appeared in the literature over the past few years (1-26). The majority of patients (who are usually homosexuals or drug addicts) present with lung and gastrointestinal infections. Here we report the CT findings in 19 patients with central nervous system symptoms associated with AIDS.

### MATERIALS AND METHODS

The hospital records of 19 male patients with documented CNS involvement in the setting of homosexuality and intravenous drug abuse were reviewed. Their ages ranged from 26 to 56 years, with only three patients over the age of 40. Eighteen were homosexual and five were intravenous drug abusers. All patients were anergic. In 14 patients there was a prior history of either Kaposi sarcoma or pulmonary and gastrointestinal infections, including *Pneumocystis carinii*, cytomegalic virus, amebiasis, giardiasis, and candidiasis. We analyzed the clinical, laboratory, and radiologic findings. For the CT findings, the primary emphasis was on determining the number and location of lesions, enhancement characteristics, and residual changes.

### RESULTS

Neurologic findings were characterized by encephalopathy in 13 patients and focal findings in six patients. Ten patients demonstrated one or more structural lesion on CT, while in nine the CT scans were either normal or showed only nonspecific atrophy and mild ventricular enlargement.

Of the ten patients with structural lesions on CT, there were seven with toxoplasmosis, one with lymphoma, one with progressive multifocal leukoencephalopathy (PML), and one with a nonspecific encephalitis. The initial CT findings and clinical data in these ten patients are summarized in TABLE I.

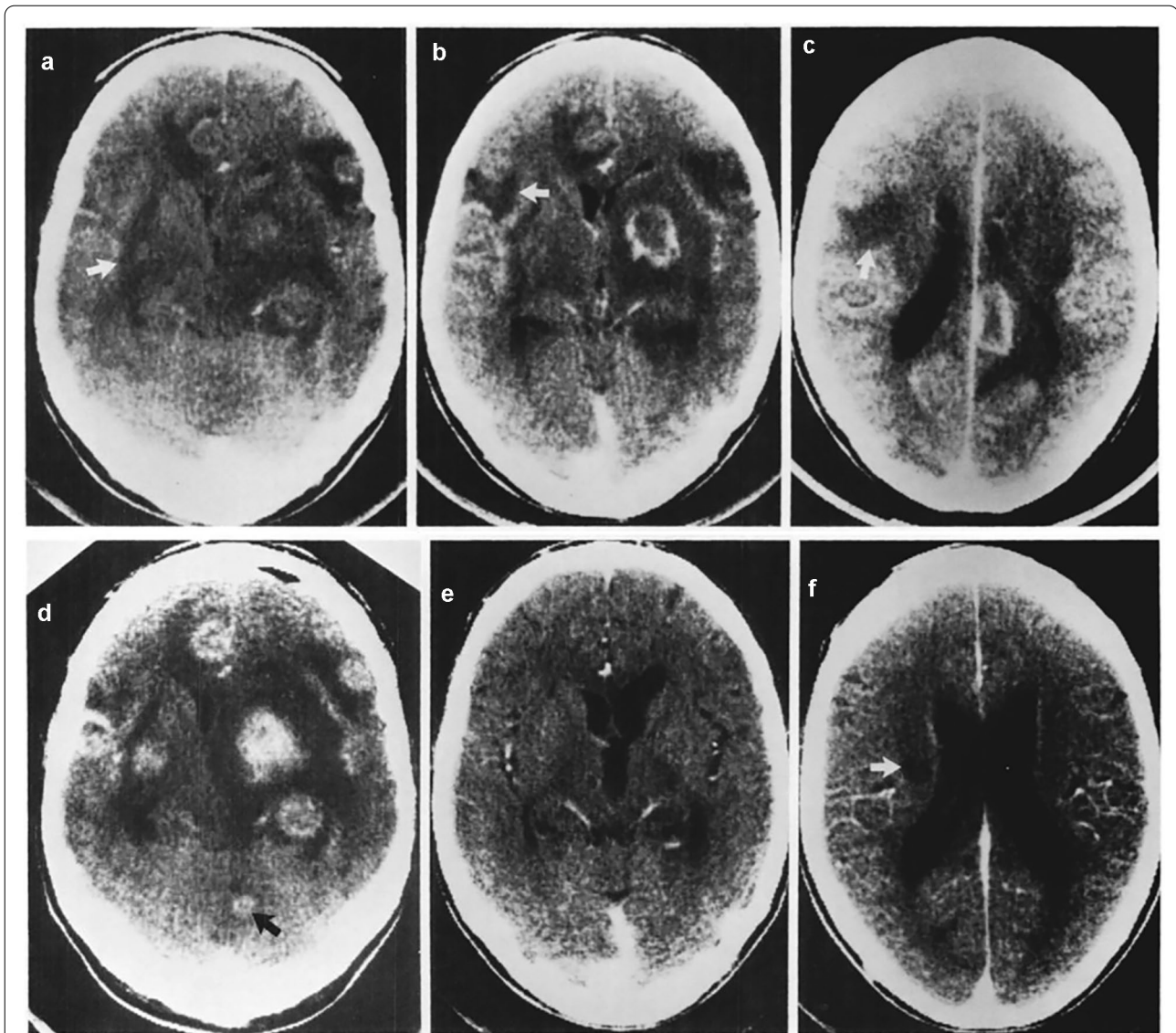
**Fig. 2** Title page on central nervous system infections. (Reprinted with permission from Whelan MA, Kricheff II, Handler M, et al. Acquired immunodeficiency syndrome: cerebral computed tomographic manifestations. *Radiology*. 1983;149(2):477-84.)

mortality barely declined. Bowen et al. [5] also concluded that CNS-opportunistic infections remained a major cause of morbidity and mortality in individuals positive for human immunodeficiency virus (HIV) and those with AIDS. They also emphasized that most treatments were administered in the absence of any controlled study or even phase 2 or 3 trial.

The emerging radiologic picture of CNS involvement revealed bilateral ring-enhancing lesions or solitary enhancing lesions associated with *Toxoplasma gondii* or Herpes simplex focal infection. The combination of Kaposi sarcoma, *Toxoplasma gondii*, and brain abscess was noted by Vilaseca et al. [6]. Disseminated toxoplasmosis, toxoplasmic encephalitis, and petechial hemorrhages were commonly seen. Multiple cerebral hemorrhages due to

*Toxoplasma gondii* were found, at least in one case report, as the first AIDS-defining condition [7]. Hemorrhages were typically associated with toxoplasma, but cerebral infarcts also became more frequently described, often in the setting of nonbacterial thrombotic endocarditis or disseminated intravascular coagulopathy [8]. Mizusawa et al. [8] suggested that 33% of patients with AIDS, after detailed postmortem examination, had a cerebral infarct related to nonbacterial thrombotic endocarditis, which was countered by a series of nearly 1400 patients with asymptomatic HIV infection with no reports of intracerebral hemorrhage or cerebral infarction after a 2-year follow-up [9].

Since the initiation of antiretroviral therapy, current concern is the risk of developing immune reconstitution



**Fig. 3** Patterns on computed tomography scan in the early described cases. (Reprinted with permission from Whelan MA, Kricheff II, Handler M, et al. Acquired immunodeficiency syndrome: cerebral computed tomographic manifestations. *Radiology*. 1983;149(2):477–84.)

inflammatory syndrome (IRIS). IRIS shows worsening after initial stabilization; magnetic resonance imaging (MRI) findings typically show leptomeningeal and even perilesional enhancement and edema in patients with cryptococcal IRIS.

Prevalence estimates from clinical and pathological series suggest that up to 5% of all persons infected with HIV will develop PML. The usual first step in confirming the diagnosis is to test CSF by polymerase chain reaction for the presence of JCV DNA. The assay result is positive in approximately 70–90% of patients not taking ART, for whom a positive result can be considered diagnostic in the appropriate clinical context. No specific therapy exists

for JCV infection or PML. Intravenous and intrathecal cytarabine and cidofovir are neither effective nor recommended. A promising report of long-term survival of a patient with PML in the setting of hematologic malignancy treated with nivolumab [10] was shortly followed by a case series on patients with PML treated with pembrolizumab [11, 12] and nivolumab [13], both antibodies to PD-1, suggesting stabilization or improvement in some patients. Paraclinical markers reported were also supportive of survival. A robust influx of CD4 and numerous CD8 cells may precipitate a clinical decline not explained by the natural course of PML. Similarly, the paradoxical deterioration here is from IRIS.

The marked clinical and MRI worsening that occurs during IRIS remains very worrisome to clinicians, but IRIS is an unavoidable consequence of treating PML. Nevertheless, treatment cannot be delayed because delay leads to a generation of additional JC antigens and accumulation of permanent brain injury from JCV. Others have emphasized that PML IRIS may be recognized by T2 bright punctate perivascular lesions on MRI (“starry sky”) [14].

During a new pandemic, it is useful to revisit prior pandemics, and certainly the AIDS epidemic has been well documented. Consultations for neurologists and, later, neurointensivists rapidly increased in these early years and to an extent we have not seen later in other outbreaks.

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