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Progressive multifocal leukoencephalopathy in acquired immunodeficiency syndrome: Explaining the high incidence and disproportionate frequency of the illness relative to other immunosuppressive conditions

Joseph R Berger

Department of Neurology, University of Kentucky College of Medicine, Lexington, Kentucky, USA

In the era of the AIDS pandemic, progressive multifocal leukoencephalopathy (PML) has ceased being a rare disease. Prevalence estimates from clinical and pathological series suggest that up to 5% of all HIV-infected persons will develop PML. The extraordinary frequency with which PML attends HIV infection vastly exceeds its appearance in association with other predisposing conditions and has resulted in it no longer being considered a rare disorder. Why PML appears to be far more common with AIDS than with other underlying immunosuppressive conditions remains unexplained. Potential explanations include an alteration of the CNS milieu by HIV facilitating JC viral entry into the brain and activation of the JCV by HIV proteins, e.g., tat, and by inflammatory byproducts of HIV infection. It is quite likely that multiple diverse mechanisms are at play. *Journal of NeuroVirology* (2003) **9(suppl. 1),** 38–41.

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Introduction

The human immunodeficiency virus (HIV) pandemic has become the most common underlying predisposing illness for progressive multifocal leukoencephalopathy (PML) and has changed the frequency with which this brain disease has been observed. From the time of its initial description in 1958 (Astrom *et al*, 1958) through the beginning of the acquired immunodeficiency syndrome (AIDS) pandemic in 1981, PML was chiefly observed in the setting of lymphoproliferative disorders. However, since the AIDS pandemic, the immunosuppression of HIV infection has set the stage for the overwhelming majority of cases of PML. The frequency with which PML occurs has increased dramatically consequent to the AIDS pandemic and the numbers of persons developing PML in association with HIV infection seems disproportionately large relative to the numbers of persons with other conditions predisposing to it, e.g., malignancy, transplantation, autoimmune disorders, etc.

PML in the pre-AIDS era

The seminal description of PML was by Aström, Mancall, and Richardson in 1958 (Astrom *et al*, 1958). They described three patients with a unique demyelinating disease of the brain and underlying

Address correspondence to Dr. Joseph R. Berger, Department of Neurology, University of Kentucky College of Medicine, Kentucky Clinic L-445, Lexington, Kentucky 40536-0284, USA. E-mail: jrbneuro@pop.uky.edu

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lymphocytic leukemia or lymphoma (Astrom *et al*, 1958). From 1958 to the early 1980s, reports of PML demonstrated that it chiefly occurred in the setting of cellular immunosuppression and most often with lymphoproliferative disorders (Brooks and Walker, 1984). An extensive review of PML conducted in 1984 reported on 113 published reports and case series from 1958 to 1984 and incorporated unreported cases from the authors' personal experience as well. A total of 230 cases were identified, of which 40 were pathologically and virologically confirmed and 69 were pathologically confirmed (Brooks and Walker, 1984). The most common underlying illnesses for this patient population were lymphoproliferative diseases. This spectrum of diseases accounted for 62.2% of all cases. Other predisposing disorders included myeloproliferative diseases (6.5%), carcinoma (2.2%), and granulomatous and inflammatory diseases (7.4%). In 5.6% of patients with PML, no underlying immunosuppressive disorder was identified.

In this series (Brooks and Walker, 1984), a broad spectrum of congenital and acquired immune deficiency states accounted for 16.1% of the associated diseases. The most common immunodeficiency state predisposing to PML in this series was systemic lupus erythematosis, accounting for 6.2% of the total cases. Renal transplantation slightly exceeded AIDS as an underlying disorder predisposing to PML and only 3.0% of the total number of cases were the consequence of the latter (Brooks and Walker, 1984). The authors cited the only two cases of PML associated with AIDS that had been published to that time (Miller *et al*, 1982; Bedri *et al*, 1983) and appeared to have added other cases personally observed to arrive at 3.0% of the total observed, but did not cite the specific numbers of their cases. In the same year that this review was published, two additional cases of PML in HIV infection were published (Bernick and Gregorios, 1984; Ho *et al*, 1984); these, however, were not included in the review by Brooks and Walker. One of those cases (Bernick and Gregorios, 1984) was from the University of Miami/Jackson Memorial Hospital, a large tertiary care center in metropolitan Dade County. This case represented one of four PML patients with AIDS seen at that institution in that year (Berger *et al*, 1998). No patients with PML with underlying illnesses other than AIDS were observed in that institution during that year and from that time onwards, AIDS was overwhelmingly the most common illness associated with PML.

PML in the AIDS era

AIDS rapidly became not only the most common predisposing disorder for PML, but also changed the frequency with which PML is observed. In 1987, Berger and colleagues observed PML in 3.8% of all hospitalized AIDS patients at the University of Miami/Jackson Memorial Hospital (Berger *et al*, 1987). Although likely skewed and not fully representative of the total HIV-infected population, this number suggested that PML was not uncommon in the setting of HIV infection. Autopsy studies confirmed this high incidence in HIV infection. Among 926 patients dying with AIDS who had been reported in seven autopsy series, 4.0% had PML at the time of death (Kure *et al*, 1991). However, similar to a hospital-based series, autopsy series of this nature are likely to be skewed to higher incidences as patients with interesting illnesses, such as PML, were far more likely to come to autopsy than others. A study conducted by the Broward Medical Examiner Office in Florida was more reflective of the true incidence of PML as it was designed to study virtually all patients dying with serological evidence of HIV infection in this jurisdiction. Among 548 unselected autopsies on HIV-seropositive patients, 5.3% had pathological evidence of PML (Tate, 1994). Two separate studies (Berger *et al*, 1987; Gillespie *et al*, 1991) found that approximately 1.0% of all HIV-infected persons presented with PML as their initial AIDS-defining illness.

In a study conducted in south Florida between the years 1980 to 1994, 156 patients with PML were identified. Of these, 154 patients had AIDS-related PML. The annual rate at which PML was observed in this population is demonstrated in Figure 1. Only two patients had other underlying illnesses; one was a young woman with Hodgkin's disease and the other an adolescent with Wiskott-Aldrich syndrome (Katz *et al*, 1994). This remarkable association with AIDS relative to other potential underlying disorders occurred in a tertiary center with a large cancer and transplant population as well as a large elderly population. In comparing the 4-year intervals, 1980–1984 to 1990–1994, there was a 20-fold increase in the incidence of PML. From the late 1980s through to the end of the study, the incidence of PML associated with AIDS appeared to have reached its plateau and data from other studies have suggested that there

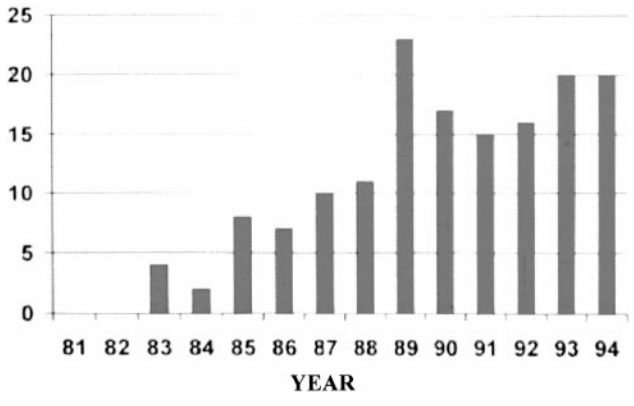

Figure 1 Data from the University of Miami/Jackson Memorial Hospital: PML cases, 1980–1994 (Berger *et al*, 1998).

has been little change since the widespread introduction of highly active antiretroviral therapy (HAART) in 1996 (Antinori *et al*, 2001; Sacktor *et al*, 2001). In many recent studies comparing the incidence of PML in the pre- and post-HAART era, the numbers of PML cases are too few to draw meaningful conclusions (Maschke *et al*, 2000; Ives *et al*, 2001).

Data derived from the diagnoses on death certificates reported to the Centers for Disease Control and Prevention (CDC) between 1979 and 1987 revealed a fourfold increase in AIDS-associated PML in the United States (Holman *et al*, 1991). By 1987, PML mortality (5.7 per 10,000,000 persons per year), chiefly the consequence of AIDS, paralleled that of Creutzfeldt-Jacob disease (4.3 to 10.0 per 10,000,000 persons per year) (Janssen 1997). This data also revealed that at least 0.72% of all persons dying with AIDS had concomitant HIV infection (Holman *et al*, 1991). However, the estimate is likely to represent a minimum estimate of the true incidence of the PML among the HIV-infected population due to the under-recognition and under-reporting of PML on death certificates (Messite and Stillman, 1996). Prevalence data obtained from a surveillance study of AIDS in the San Francisco Bay area indicated that by 1991, 0.3% (0.0–0.8) of individuals with AIDS in the San Francisco Bay area had PML (Gillespie *et al*, 1991). More recent statistics derived from a national surveillance project of the CDS in collaboration with 11 state and local health departments in which medical records of HIV-infected patients are abstracted (CDC, 1997) suggest that the prevalence of PML among adult patients with AIDS (as defined by the 1993 CDC AIDS case definition) is 2.4% (Dworkin *et al*, 1999). If these statistics are correct, given that there are approximately 330,000 persons living in the United States with AIDS (CDC, 2002) and PML generally results in death within 1 year of diagnosis, one can estimate that there are 7000 to 8000 new cases of PML among the U.S. AIDS population annually. This number would exceed the annual incidence of patients with Guillain-Barré syndrome or Huntington's disease and approach that of multiple sclerosis (Kurtzke and Kurland, 1983).

Hypotheses for the high rate of PML in AIDS

The explanation for the striking increased incidence of PML in the setting of HIV infection relative to its incidence with other immunosuppressive conditions presently remains uncertain. One possible explanation is that HIV infection results in quantitatively or qualitatively differences in immunosuppression in comparison to the other conditions. Additionally, the duration of the severe impaired cell-mediated immunity occurring in AIDS may contribute with longer durations required for the appearance of the disease. Shortly after HIV infection, the virus crosses into the brain (Lane *et al*, 1996). This passage is believed to be cell associated, presumably in infected monocytes, i.e., the "Trojan horse" mechanism. In time, productive infection of the brain is observed with the HIV-infected macrophages located preferentially in perivascular spaces. The local microenvironment created by this infection may be responsible, in part, for the high frequency of PML. In part, it may facilitate entry into the brain of JC virus (JCV)-infected B cells, perhaps by the up-regulation of adhesion molecules on the endothelial surface that assist or are required for B-lymphocyte trafficking into the brain. This mechanism might explain the low rate for the development of PML in other immunosuppressive conditions in which passage of these infected lymphocytes, which are present in the systemic circulation of as many as 30% to 50% of patients with a wide variety of immunosuppressive conditions (Tornatore *et al*, 1992), but are perhaps more commonly found in the circulating B cells of HIV-infected persons than with other immunosuppressive conditions (Dubois *et al*, 1998). Infected circulating B cells can also be observed in as many as 5% of normal individuals (Tornatore *et al*, 1992). The trafficking of B cells into the central nervous system (CNS) is poorly understood (Williams and Hickey, 1995). Activated, but not resting, B cells can bind to the extracellular matrix of endothelium via E- and P-selectins (Williams and Hickey, 1995). In preliminary studies, however, the expression of a select number of other adhesion molecules has not been detected on the endothelial cells of the brain in regions affected with PML (Nath, 2002). Alternatively or additionally, HIV proteins, e.g., tat, and the cytokines and chemokines that are elaborated in the microenvironment of HIV infection may result in transactivation of the JCV (Couraud, 1998; Persidsky, 1999; Chi *et al*, 2000; Berger *et al*, 2001) (Figure 2).

It is quite likely that the mechanisms underlying the extraordinarily high frequency with which PML

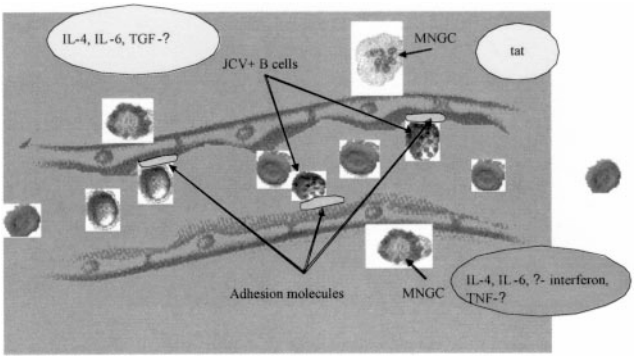

Figure 2 Brain blood vessel in patient with AIDS. Postulated mechanisms by which HIV infection alters the microenvironment of the brain to contribute to the increased risk of developing PML. MNGC = HIV-infected multinucleate giant cell; IL-4, IL-6, γ-interferon, TNF-γ = products capable of increasing the expression of endothelial adhesion molecules; IL-4, IL-6, TGF-γ, tat = products capable of transactivating JCV.

is observed in association with AIDS is multifactorial. Clarifying the roles of each of these mechanisms will help immeasurably in understanding the pathogenesis of this disorder. It will also invariably open new avenues for the prevention and treatment of PML.

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