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EDITORIAL

Progressive multifocal leucoencephalopathy: progress in the AIDS era

Progressive multifocal leucoencephalopathy (PML) has been described as a complication in various conditions which result in impaired cellular immunity—these include lymphoproliferative disorders and chronic granulomatous disorders such as sarcoidosis. Iatrogenic immunosuppression in post-transplant patients and patients undergoing cancer chemotherapy, as well as those with autoimmune disorders, is also a risk factor. The occasional case has been described in pregnant women which some may regard as being an immunosuppresssed state.[1] A review in 1984 of 230 patients found that 69% were due to lymphoproliferative or myeloproliferative disorders, 7% granulomatous disorders, 6% postrenal transplant, and 4% occurred in patients with the acquired immunodeficiency syndrome (AIDS). About 6% of all patients with PML had no identifiable evidence of immunosuppression. These were all anecdotal reports from the early 1970s.[2]

Since the onset of the AIDS epidemic in 1981, the incidence of PML has increased significantly and now human immunodeficiency virus (HIV) associated cases account for up to 85% of all cases of PML. Before the introduction of highly active antiretroviral therapy (HAART), the estimated incidence in patients infected with HIV was 4%.

HAART is the term used for a combination of three or four anti-HIV drugs from the following classes—nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transciptase inhibitors, and protease inhibitors. The widespread availability and uptake, at least in the developed world, of HAART has had a dramatic impact on morbidity and mortality of patients infected with HIV. This is, in part, due to reduction in incidence of opportunistic infections. In the period 1995 to 1997, one United States study documented a fall in the combined incidence of *Pneumocystis carinii* pneumonia, *Mycobacterium avium* complex, and cytomegalovirus infection from 21.9 per 100 person-years to 3.7 per 100 person-years.[3] In one London hospital, the number of cases of toxoxplasmosis fell from 19 cases in 1996 to five in 1998.[4] Reports pertaining to the incidence of PML since the introduction of HAART have, to date, been conflicting.

Progressive multifocal leucoencephalopathy (PML) is an acquired demyelinating disorder of the CNS caused by the JC virus.[5] This DNA virus, so labelled after the initials of the patient whose tissue was used to isolate it, is a member of the genus *Polyomavirus* in the family *Papovaviridae*, which also includes BK virus and SV 40 virus.

The clinical presentation of PML is usually one of a progressive neurological deficit resulting in a monoparesis or hemiparesis, hemianopia, or ataxia (table).[6] Despite its name, the disease is not restricted to cerebral white matter as the presentation may be with cortical deficits such as dysphasia, cortical blindness, or seizures. Cortical involvement may also be evident on MRI and in the neuropathological findings. Patients may also present with a dementing disorder with focal neurological signs. By contrast with the other causes of focal abnormalities in patients infected with HIV—toxoplasmosis and primary CNS lymphoma—there are no symptoms or signs of raised intracranial pressure or of systemic infection. There has been only one description of spinal cord involvement diagnosed at necropsy but not antemortem.[7]

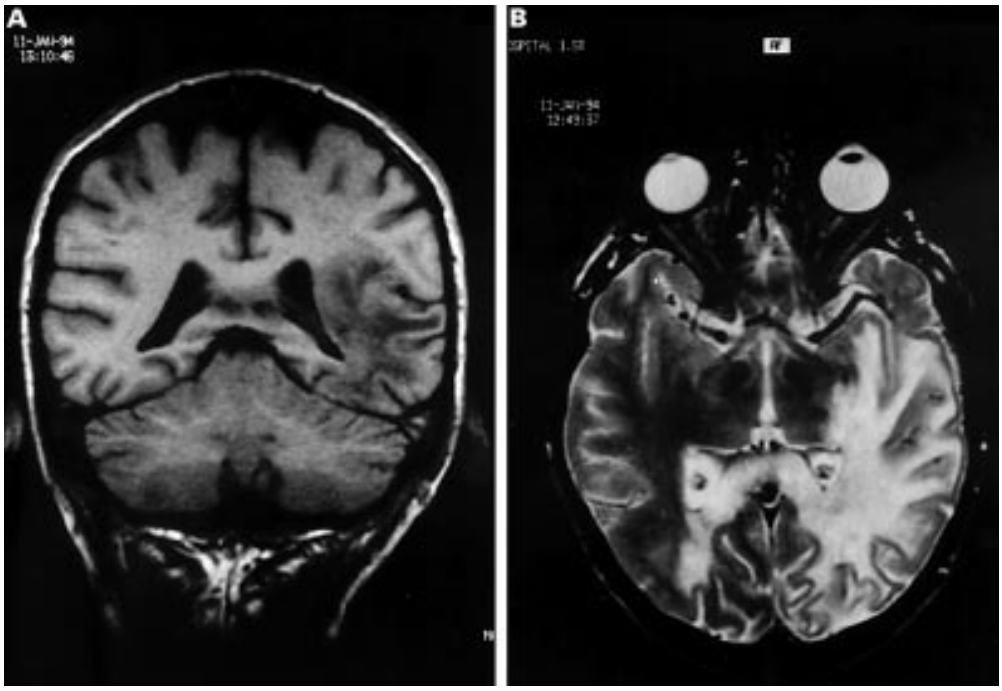
Table 1 Clinical signs and symptoms (%) of patients with PML[6]

Motor function abnormalities	67
Mental status changes	66
Hemiparesis	39
Seventh cranial nerve palsy	38
Fine coordination problems	34
Language disorders	31
Visual problems (for example, hemianopia)	30
Other cranial nerve signs	27
Ataxia	26
Headache	23
Sensory loss	18
Seizures	11

In the appropriate clinical setting, MR scans have some characteristic features—the lesions, which may be single or multiple, involve mainly white matter and may depict a scalloping at the grey/white interface due to involvement of the arcuate fibres (figure A and B).The parieto-occipital and frontal areas of the brain are most often affected. Less often, abnormalities are found in the posterior fossa, corpus callosum, thalamus, and basal ganglia. The affected areas are of low signal intensity on T1 weighted sequences. The hyperintense lesions on T2 weighted images are much more obvious and occasionally dramatic. Cranial CT shows hypodense lesions. Contrast enhancement and mass effect are seen only rarely on imaging studies.[8]

Occasionally, HIV encephalopathy may cause diagnostic confusion but clinical focal signs are rare and on imaging the abnormalities tend to be more symmetric and less discrete than in PML. On T1 weighted MRI images the low signal lesions due to PML are much more obvious than in HIV related changes.

Before and in the early years of the AIDS epidemic, a definitive diagnosis of PML was only possible by brain biopsy. The typical histological features are of areas of



MRI of PML related to HIV: (A) T1 weighted and (B) T2 weighted images.

demyelination with enlarged oligodenrocyte nuclei with inclusion particles which are seen at the edges of such lesions. Infected astrocytes, which are enlarged with bizarre nuclei, contain mitotic figures resembling areas of neoplasia. In situ hybridisation techniques confirm that the inclusion bodies consist of JC viral particles.

As 80% to 90% of the general population have been exposed to the JC virus, probably as a banal childhood upper respiratory tract infection, and have IgG antibodies against the virus, serological tests are unhelpful in making a diagnosis of PML. Standard cytochemical indices in the CSF such as cell count and protein concentration are similarly of little value as minor abnormalities such as an increased cell count and protein may be due to HIV itself. In one study of 11 patients, seven had a normal CSF. Three patients had a pleocytosis ranging from 4 to 10 mononuclear cells/mm^3 and three had an increased protein concentration (range 0.53–0.67 g/l). The CSF glucose concentration was within the normal range in all.[9] The JC virus has never been cultured, nor have any viral antigens been identified in the CSF. The detection of intrathecal antibody has a sensitivity of 67% and a specificity of 99% in non-HIV infected patients with PML.[10]

In common with other microbial diseases, the use of DNA amplification techniques, in particular the polymerase chain reaction (PCR), has made a significant impact on the diagnosis of PML. Most studies suggest a sensitivity of around 75% with a specificity of between 90% and 99% for detection of JC viral DNA in the CSF.[11] The low sensitivity may be due to the fact that the virus is mainly contained intracellularly with few virions free in CSF. The high specificity has therefore obviated the need for brain biopsies in many patients. However, the false negative rate of around 25% means that a negative result does not exclude the diagnosis and it may be necessary to repeat the lumbar puncture or carry out a brain biopsy. Recently, semiquantitative measurements of JC viral DNA load in CSF have been shown to correlate with survival and may potentially be used as a method of monitoring the disease response to any therapeutic interventions, in addition to the clinical and radiological assessments.[12] Although serial MRI may be a useful technique for follow up, changes are non-specific and may be difficult to distinguish from, for example, HIV encephalopathy especially when both coexist.

It has been demonstrated that regardless of immune status, JC virus remains latent in the kidneys and may be detected in urine. Whether PML results from reactivation of latent virus in the brain or haematogenous spread remains unclear. There is conflicting evidence as to whether JC viral DNA is present within the brains of non-immunocompromised patients. However, the development of so called primary PML in patients with no evidence of immunosuppression would suggest that the virus may lie dormant within the nervous system. In favour of the "haematogenous spread" argument, Koralnik *et al* have demonstrated that JC virus detection in plasma and in peripheral blood mononuclear cells correlates with immunosuppression although not with PML.[13] One other piece of evidence for this hypothesis is the pathological finding that lesions of PML have a predeliction for the grey/white interface around end arterioles.

The prognosis of patients with PML is appalling for both HIV and non-HIV associated patients with median survival figures between 6 and 9 months. However, there are anecdotal reports of prolonged survival. In the pre-AIDS era one patient survived for 19 years.[14] Berger *et al*, studying a group of HIV associated cases of PML with prolonged survival (defined as greater than 12 months) found the following factors to be predictive when compared with those who survived less than 12 months: PML as AIDS defining diagnosis, high CD4 count (>300 cells/mm) at onset and lesion enhancement on imaging. Five out of seven patients in this group showed clinical and radiological improvement which seemed unrelated to any treatment—either JC virus specific or anti-HIV.[15] This spontaneous remission effect, together with the paucity of cases before the advent of HIV infection has made it difficult to interprete anecdotal reports of benefit with various therapeutic regimens.

Because the nucleoside analogue cytosine arabinoside (Ara-C) was effective against other DNA viruses such as herpes simplex virus, it seemed reasonable to use the drug in patients with PML. Although initial reports suggested benefit, a multicentre trial of 57 patients infected with HIV

with biopsy proved PML found no significant difference in survival when three groups were compared: antiretroviral therapy alone, antiretroviral therapy plus intavenous Ara-C, and antiretroviral therapy plus intrathecal Ara-C.[16] Most patients (88%) died of their PML disease rather than any other complication of HIV infection.

In a similar fashion, the use of α-interferon in PML was prompted by its efficacy in the treatment of anogenital warts induced by human papilloma virus. The mechanism by which α-interferon affects the disease process is unclear but interferons are purported to have an antiviral effect as well as having an immune enhancing effect by, for example, augmenting cytotoxic T lymphocytes.

The largest study to date was a retrospective open labelled observational study, with 32 patients in the untreated and 21 in the treated arms.[17] The dose of the subcutaneously administered α-interferon (usually type 2b) was either 3 million units given daily or 5 million units three times a week. The median survival time in the treated group was significantly higher—325 days versus 175.5 days, (p=0.03). In the treated group, seven out of 21 patients showed striking clinical improvement compared with four of the 32 in the untreated group. In the untreated group the improvement was usually transient. Furthermore, two of the seven responders showed improvement on MRI whereas only one in the untreated group improved radiologically but with no signs of clinical benefit.

The side effects of interferon treatment encountered were leucopenia, pancytopenia, depression, and fatigue. This resulted in transient cessation of the drug in two patients and discontinuation in another two. A randomised controlled trial with interferon is now necessary.

Cidofovir, a nucleoside analogue with in vitro and in vivo activity against herpes viruses, is licensed for treatment of cytomegalovirus retinitis; in vitro activity against JC virus has also been demonstrated. Recently, some case reports have suggested benefit.[18 19] As a result a multicentre, randomised open label European trial has been set up to evaluate the efficacy and safety of the drug in HIV associated PML, comparing remission rates in immediate versus deferred treatment arms. Patients will continue with optional antiretroviral therapy.

The incidence of PML in AIDS is seemingly much higher than in any other disorder of immunosuppression raising the possibility, quite apart from the profound immunosuppression found in these patients, of interaction between the JC and HIV viruses. It has been demonstrated that the HIV nuclear protein Tat can increase the transcriptional activity of JC virus in glial cells.[20] This, together with the reports of improvement after cessation of immunosuppressive therapy in non-AIDS patients made the early reports of improvement in patients with PML on HAART plausable.[21] The largest study, by Clifford *et al*, compared a cohort of 25 patients with HIV associated PML to historical controls.[22] The median survival in the first group was 46.4 weeks compared with 11 weeks in controls. Although there are obvious limitations to such a study, including the fact that four patients were also on additional treatment directed against JC virus (α-interferon and cidofovir), it would seem reasonable to recommend aggressive antiretroviral treatment in patients with HIV associated PML. However, as the authors point out, 15 of the 25 patients were on HAART at the time of diagnosis with significantly reduced plasma HIV viral load—a surrogate marker now used routinely to monitor the efficacy of antiretroviral treatments. This study did not examine treatment effect on neurological or radiological improvement.

A French retrospective study of 31 patients with PML treated with HAART confirmed the increased survival in this group. However, it found no evidence of change in the 18 survivors, as a group, in the expanded disability status scale (EDSS) scores at baseline and at the study end point.[23] Individually, six patients were worse, eight improved, and four remained stable.

Thus, although it seems necessary to reconsitute the immune system as far as possible this strategy alone is clearly inadequate. Specific anti-JC virus treatments are also required in a two pronged attack in the treatment of patients with HIV related PML.

Since the AIDS epidemic, with the increase in numbers of patients with PML, there has been significant progress in research into the biology of JC virus and with the diagnosis of the condition without the need for brain biopsy. In addition, there are promising treatment regimens on the horizon. These, hopefully, will be of benefit not just to patients with HIV but also to those who develop PML as a result of other diseases.

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