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The evolving face of human immunodeficiency virus–related progressive multifocal leukoencephalopathy: Defining a consensus terminology

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There is a need for consistent definition of human immunodeficiency virus (HIV)-associated cases of progressive multifocal leukoencephalopathy (PML), especially following the profound disease changes that have resulted from the use of highly active antiretroviral therapy (HAART). According to the criteria used for diagnosis, PML cases should be either referred to as "histology-confirmed," with evidence of JC virus (JCV) infection in brain, "laboratory-confirmed," with detection of JCV DNA in cerebrospinal fluid (CSF), or "possible," in the presence of typical clinical and radiological picture, but no demonstration of JCV infection. Disease outcome should be defined by the evidence or lack of evidence of disease activity, rather than using survival or other variables. Disease activity should be based on clinical (scored neurological examination), radiological (magnetic resonance imaging), and virological (JCV DNA levels in CSF) indicators, to be assessed regularly, e.g., every 3 months until evidence of disease arrest or death. Furthermore, parallel assessments of other HIV-associated manifestations, including CD4+ cell counts and viral load, are required. A standard patient classification would be helpful for clinical management of PML patients, for their inclusion in clinical studies, and also will increase our current knowledge of PML and its evolution in relation with HAART. *Journal of NeuroVirology* (2003) **9(suppl. 1),** 88–92.

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Historical background

Although the first descriptions of a disease resembling what we now call progressive multifocal leukoencephalopathy (PML) have appeared in the medical literature since 1930 (Hallervorden, 1930), the term PML was proposed for the first time in 1958 (Astrom *et al*, 1958). At that time already, the disease was suspected to be of viral origin, because of the histological demonstration of nuclear inclusions in oligodendrocytes. A causative role for a polyomavirus infection was suggested in 1965, following the observation of polyomavirus-like particles in these cells on electron microscopy (ZuRein and Chou, 1965; Silverman and Rubinstein, 1965). In 1971, the polyomavirus JC virus (JCV) was isolated from the brain of a patient who died of PML (Padgett *et al*, 1971). Likely, PML would have been called *JCV encephalopathy* or *JCV leukoencephalopathy* if its

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etiology had been known at the time the syndrome was first described. However, the term PML is now widely used and still reminds us of the most prominent features of this disease.

Nevertheless, the experience collected over the last decades, especially with observation of human immunodeficiency virus (HIV)-associated cases, shows that PML does not always affect only the white matter and it is not invariably a multifocal or even a fatal disease. For instance, involvement of the gray matter is occasionally observed (Sweeney *et al*, 1994). Also, the disease is frequently a unifocal disease at its onset, both clinically and radiographically. Finally, although PML is virtually always fatal in the context of a severe immunodeficiency, there are case reports of long-lasting periods of clinical remission and even evidence of spontaneous arrest of the disease (Price *et al*, 1983).

PML, HIV infection, and HAART

Historically, the prognosis of PML was very poor in patients with HIV infection, with death most frequently ensuing within 3 to 4 months from the time of first disease manifestation (Berger *et al*, 1998). None of the proposed treatments, including cytarabine, alpha-interferon, and cidofovir, has ever convincingly influenced disease progression in careful prospective trials (Hall *et al*, 1998; Geschwind *et al*, 2001; Gasnault *et al*, 2001; Marra *et al*, 2002). In contrast, the outcome of PML has changed drastically following the advent of highly active antiretroviral therapy (HAART). Cohort studies indicate a significant increase of survival of HAART-treated PML patients compared to historical cases (Clifford *et al*, 1999; Dworkin *et al*, 1999; Tassie *et al*, 1999; De Luca *et al*, 2000). This increase is due to apparent disease stabilization in approximately one half of the patients. However, in the other half of the cases, survival is not longer than it used to be before the use of HAART.

Different terms have been used in the recent medical literature to describe these two groups of HAART-treated PML patients, based on their disease outcome. These have included the following definitions: *responders* versus *nonresponders*, *progressors* versus *nonprogressors*, *survivors* versus *nonsurvivors*, or *long-* versus *short-survivors*. Most of these definitions sound inadequate or unpractical. For instance, the terminology *responders* versus *nonresponders* might lead to confusion about response to HAART rather than evolution of PML. Viroimmunological response to HAART in terms of decreased viral load and increased CD4+ is not necessarily associated with good PML outcome. In turn, the use of the *nonprogressor* versus *progressor* categories would lead to the redundant *progressive PML* or the oxymoron *nonprogressive PML*. On the other hand, the practical value of survival classes is limited, and in fact given the human condition, it is only a matter of time before all patients fit the nonsurvivor class. Patients with classically progressive disease may survive for more than 1 year; in contrarst, patients who survive PML may die soon afterwards of other HIV-related conditions. Furthermore, these terms can only be applied retrospectively, and therefore are of reduced value for patient management. Establishing a consensus in terminology and definition criteria for PML and PML outcome would be useful for management of patients and in multicenter clinical studies. Systematic description of disease evolution will clarify the course of HIV-induced PML in HAART-treated patients.

Proposal for a terminology for PML diagnosis and outcome

Definition of PML based on diagnostic criteria
Preliminary to the proposal of a terminology for disease outcome is the need of correctly identifying PML cases. The following diagnostic categories are proposed:

- Histology-confirmed PML: Cases with progressive uni- or multifocal neurological disease, typical magnetic resonance imaging (MRI) lesions, and brain biopsy (or postmortem examination), showing typical pathological features with JCV confirmed either immunohistochemically or by *in situ* hybridization.
- Laboratory-confirmed PML: Cases with JCV DNA in cerebrospinal fluid (CSF) by nucleic acid amplification methods in the setting of appropriate clinical disease and imaging findings.
- Possible PML: All of the clinical and radiological findings consistent with PML, but in the absence of both histological confirmation and JCV demonstration in CSF. These cases might become confirmed upon a positive JCV result on repeat CSF analysis.

Incidentally discovered white matter lesions at MRI without active associated neurological disease, incidental JCV polymerase chain reaction (PCR)-positive CSF without active clinical disease or MRI findings are improbable for PML, and although interesting to study, they should not be considered representative of the disease PML.

It has been agreed that belonging to one of the first two categories—histology-confirmed or laboratory-confirmed PML—is required for patient inclusion in clinical trials. However, it was argued whether the detection of JCV DNA in CSF could hold the same degree of certainty required for a "definite" diagnosis of PML as for brain biopsy. Therefore, the proposed terminology reflects the ongoing debate by not being hierarchic in its form. Nevertheless, it provides a means to reach consistent case descriptions as well as to help select patients for clinical studies. The following comments summarize the main pros and cons of PML diagnostic procedures that have been discussed.

Histological diagnosis of brain tissue obtained by stereotactic brain biopsy is the standard procedure for establishing an etiologic diagnosis of PML. In acquired immunodeficiency syndrome (AIDS)-related focal lesions, the brain biopsy has a sensitivity of 64% to 96%, with "sampling errors" being the most frequent cause for lack of identification of an etiology. On the other hand, specificity is virtually 100% (Vinters *et al*, 1989; Levy *et al*, 1992; Holloway and Mushlin, 1996; Antinori *et al*, 1997). Brain biopsy is an invasive procedure and it has been associated with 0% to 2% mortality, 0.5% to 9% major morbidity, and 2% to 4% minor morbidity (Levy *et al*, 1992; Holloway and Mushlin, 1996; Antinori *et al*, 1997). Because of its invasiveness, elevated costs, and structural requirements, coupled with the historically poor prognosis of PML, patients and physicians have often been reluctant to perform this investigation.

JCV DNA detection in CSF enables rapid and less invasive etiological diagnosis of PML. A number of case-control studies have shown that this method is 72% to 92% sensitive, with an increased likelihood of a positive finding with disease progression. Specificity has been found to be of 92% to 100% (reviewed in Cinque *et al*, 1997). However, a positive JCV DNA result can occasionally be found in patients with clinical manifestations inconsistent with PML (Ferrante *et al*; 1998, Dörries *et al*, 2002; Clifford, personal observation). It is possible that such apparently aberrant findings may disclose a role for JCV in central nervous system (CNS) diseases other than PML or may result from JCV DNA detection in latently infected CSF lymphocytes by an excessively sensitive assay. In any case, this possibility underscores the need for cautious interpretation of CSF findings in the clinicoradiological context. On the other hand, it points to the urgency of performing interlaboratory quality controls for standardization and optimization of diagnostic nucleic acid amplification techniques (Weber *et al*, 1997).

Definition of PML outcome based on disease activity
PML can be classified as *active* or *inactive* based on clinical, radiological, virological, and pathological criteria. Such classification, however, implies that disease activity is evaluated serially, at least for the first three types of criteria. At baseline, only the clinical activity can be estimated by history, but subsequent follow-up allows disease classification by imaging and virological criteria as well. Given the aggressive course of this disease, 3-month intervals are probably the maximal interval useful for monitoring disease activity, and much shorter intervals may result in unequivocal definition of activity. In this regard, description of PML course over 3-month blocks is proposed until death or evidence of PML inactivity.

Clinical criteria: PML is considered *active* on presentation if the disease has worsened during the past 3 months or there is clinical evidence of more severe and wider involvement of the brain on subsequent evaluations. Cases not fitting these criteria are considered as *inactive* PML, and include those with either stable or regressing neurological symtoms. Such evaluation should use a standard scored neurological examination, such as that employed in the ACTG 363 study on the clinical efficacy of cidofovir in HIV-associated PML (Marra *et al*, 2002), or the expanded disability status scale (EDSS) (Kurtzke, 1983).

MRI criteria: PML is considered *active* in the presence of MRI lesions progressing in terms of their number, volume, or both. Further MRI indicators of disease activity, e.g., increased T1 hypointensity or MR spectroscopy, also deserve consideration. PML is *inactive* in patients who do not develop new lesions or enlargement of known lesions, but rather atrophic changes of old PML lesions (Thurnher *et al*, 2001). Activity and direction of change of the MRI parameters should be defined over a maximal interval of 3 months. Note that paradoxical worsening of MRI lesions may precede radiological improvement or stabilization in patients who are already clinically stable. This is may be an HAART-induced immune reconstitution event.

Virologic criteria: Quantification of JCV DNA load in CSF at the same intervals as clinical and MRI evaluation may provide additional evidence of disease activity. There is some evidence of an association between JCV DNA load in CSF and disease outcome (Yiannoutsos *et al*, 1999). Furthermore, current experience suggests that JCV DNA levels either increase, remain stable, or fluctuate over time in patients with *active* PML (Eggers *et al*, 1999). On the contrary, patients without evidence of disease activity usually show a decrease of JCV DNA levels until they are cleared from CSF (Garcia de Viedma *et al*, 1998; Giudici *et al*, 2000). Because approximately one third of patients may not yield JCV DNA in CSF at the time of PML diagnosis, this indicator may be missing in the evaluation of PML activity. A number of quantitative assays are in use for measurement of JCV DNA load, therefore their standardization is an absolute requirement.

Pathological criteria: In a relevant number of patients the diagnosis of PML is achieved by means of brain biopsy. Because a significant proportion of PML patients would eventually die of PML, postmortem brain examination might provide further evidence of disease activity. Change of *active* to *inactive* PML might also be theoretically documented at postmortem examination in patients with brain biopsy-proven PML who die of PML-unrelated events. Although active PML is defined by the presence of JCV-infected glial cells, bizarre astrocytes, and lipid-ladden macrophages in the context of demyelination, inactive PML will be characterized by presence of demyelinated areas withouth evidence

of JCV antigen by immunohistochemistry. A regression of astrocytic and oligodendroglial changes, and disappearance macrophages and JCV antigen, are described in at least one HIV-negative biopsy-proven PML case in which postmortem examination failed to reveal typical PML changes (Price *et al*, 1983).

In addition to accurate evaluation of these indicators of PML activity, it is important to track the course of other HIV-related events, including clinical manifestations, and with particular attention to CNS complications other than PML. These might obscure the PML course or, on the other hand, be erroneously interpreted as PML-related events. Furthermore, CD4+ cell counts and plasma HIV-1 load determination are useful to interpret PML changes in the context of HAART-induced immune reconstitution.

Conclusions

In summary, patients with *active* PML will have clinical, radiological, virological, and possibly pathological evidence of disease activity through the course of their illness. In our clinical experience, the great majority of these patients will progress and die over a few months' time, although PML might progress more slowly in a smaller proportion of cases.

In contrast, patients with *inactive* PML will lack clinical, radiological, virological, and possibly pathologically evidence of disease activity. Most likely, the virus is no longer replicating in the brain and patients are left with neurological sequelae, resulting from prior permanent destruction of brain tissue. Stabilization of PML may occur at variable time during the course of PML, irrespective of the severity of the neurological involvement. However, clinical experience suggests that it is usually reached within a few months from the onset of disease. Patients with inactive PML experience virtually no progression over years of follow-up, even following withdrawal of HAART (Giudici *et al*, 2000), and JCV-specific cytotoxic T lymphocytes can be detected in their peripheral blood mononuclear cells (PBMCs) (Koralnik *et al*, 2002). Although cases of PML relapse are reported following initial remission (Corral *et al*, 2002), neurological progression is more likely due to a superimposed new process, or changing neuromuscular function.

Clinical and biological studies of PML would greatly benefit from the use of a consistent terminology for definition of PML outcome, especially in HAART-treated patients. The use of terms relating to disease activity is desirable for both practical reasons and because these seem to best reflect the biological events underlying the clinical manifestations of PML. Establishing this standard terminology will also be helpful in tracking changing patterns of JCV-associated CNS disease in the future, as it is likely to continue to change with evolution of anti-HIV therapy and, hopefully, development of anti-JCV specific treatments.

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