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Original Article

JC virus-associated central nervous system diseases in HIV-infected patients in Brazil: clinical presentations, associated factors with mortality and outcome

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ABSTRACT

Introduction: Several presentations of neurologic complications caused by JC virus (JCV) in human immunodeficiency virus (HIV)-infected patients have been described and need to be distinguished from the "classic" form of progressive multifocal leukoencephalopathy (PML). The objectives of this study were: 1) to describe the spectrum and frequency of presentations of JCV-associated central nervous system (CNS) diseases; 2) identify factors associated with in-hospital mortality of patients with JCV-associated CNS disease; and 3) to estimate the overall mortality of this population.

Material and methods: This was a retrospective study of HIV-infected patients admitted consecutively for JCV-associated CNS diseases in a referral teaching center in São Paulo, Brazil, from 2002 to 2007. All patients with laboratory confirmed JCV-associated CNS diseases were included using the following criteria: compatible clinical and radiological features associated with the presence of JCV DNA in the cerebrospinal fluid. JCV-associated CNS diseases were classified as follows: 1) classic PML; 2) inflammatory PML; and 3) JC virus granule cell neuronopathy (GCN).

Results: We included 47 cases. JCV-associated CNS diseases were classified as follows: 1) classic PML: 42 (89%); 2) inflammatory PML: three (6%); and 3) JC virus GCN: four (9%). Nosocomial pneumonia ($p = 0.003$), previous diagnosis of HIV infection ($p = 0.03$), and imaging showing cerebellar and/or brainstem involvement ($p = 0.02$) were associated with in-hospital mortality. Overall mortality during hospitalization was 34%.

Conclusions: Novel presentations of JCV-associated CNS diseases were observed in our setting; nosocomial pneumonia, previous diagnosis of HIV infection, and cerebellar and/or brainstem involvement were associated with in-hospital mortality; and overall mortality was high.

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Introduction

The incidence of progressive multifocal leukoencephalopathy (PML) has decreased in the highly active antiretroviral therapy (HAART) era, although not to the same extent as that of other opportunistic infections of the central nervous system (CNS).[1,2] In addition, PML appears to be far more common with acquired immunodeficiency syndrome (AIDS) than with other underlying immunosuppressive conditions.[3]

In Brazil, PML constitutes the fourth most frequent opportunistic complication after cerebral toxoplasmosis, cryptococcal meningoencephalitis, and CNS tuberculosis, the three more frequent neurological opportunistic infections in our setting.[4,5] In recent years, novel presentations of JCV-associated CNS diseases have been described and need to be distinguished from the "classic" manifestations of PML. Scarce data are available about these other presentations and the clinical outcome of neurologic complications caused by JCV-associated CNS diseases in HIV-infected patients from Brazil. The objectives of this study were: 1) to describe the frequency of presentations of JCV-associated CNS diseases; 2) to identify associated factors with in-hospital mortality of patients with JCV-associated CNS diseases; and 3) to estimate the overall mortality of this population.

Patients and methods

This is a retrospective study of HIV-infected patients admitted consecutively for JCV-associated CNS diseases at Instituto de Infectologia Emílio Ribas, a referral teaching center in São Paulo, Brazil, between January 2002 and December 2007. All patients with laboratory-confirmed JCV infection were included using the following criteria: compatible clinical and radiological features (computerized tomography – CT – or magnetic resonance imaging – MRI) associated with the presence of JCV DNA in CSF.[6-8] JCV-associated CNS diseases were classified at admission as follows: 1) classic PML; 2) PML-immune reconstitution inflammatory syndrome (IRIS); and 3) JCV granule cell neuronopathy (GCN). Classic PML typically presents with subacute neurological deficits including hemiparesis or monoparesis, altered mental status, appendicular or gait ataxia, and visual symptoms.[7] Inflammatory PML occurs in the setting of a recovery of the immune system marked by an increase in CD4+ cell count and a decrease in HIV plasma viral load.[6-8] Patients with GCN exclusively presented cerebellar syndrome and cerebellar atrophy in MRI without white matter lesions.[7] All patients received HAART after JCV-associated CNS diseases diagnosis (de novo or intensification of treatment). Brainstem involvement was defined by the presence of clinical evidence of at least one of the following symptoms: oculomotor palsies, vestibular syndrome with dizziness, nausea, positional vomiting and nystagmus, swallowing disorders related to bulbar or pseudobulbar syndrome, stupor, and clouding of consciousness.[9] Brainstem involvement was confirmed by the presence of brainstem demyelination on brain MRI.

Univariate analysis was used to identify variables associated with death during hospitalization. A p-value ≤ 0.05 was considered significant. Patients with cerebellar and brainstem involvement were grouped into the same category. All patients included in this study were followed up until discharge or in-hospital death. Some of the survivors were followed in our Outpatient Care Unit. In order to estimate the proportion of survivors one year after the diagnosis of JCV-associated CNS diseases, a telephone call to patients without follow-up in our institution was performed. This study was approved by the Institutional Review Board of our center.

Results

We included 47 cases (median age: 37 years-old, male: 70%). 42 patients (89%) had previous diagnosis of HIV infection. The median time from the beginning of the symptoms until the diagnosis was 39 days. Most frequent clinical manifestations were: speech disorder (64%), altered mental status (57%), focal weakness (49%), walking disturbances (43%), mental slowing (36%), cerebellar syndrome and/or brainstem involvement (36%), visual disturbances (24%), and seizures (19%).

The median CD4+ cell count was 65 cells/mm^3. The CD4+ cell count was categorized as follows: < 50 cells/mm^3 = 26 (55.3%), 51-100 cells/mm^3 = eight (17%), 101-200 cells/mm^3 = 10 (21.3%), and > 200 cells/mm^3: three (6.4%) cases.

Computerized tomography scans were performed in all cases and showed hypodense areas in the white matter in 91% (n = 42) of cases, and 71% (n = 30) of these cases presented multifocal lesions. CTs with cerebellar and/or brainstem alterations were observed in 13 (29%) cases: hypodense areas in nine cases and cerebellar atrophy in five cases (one case simultaneously had hypodense areas in the cerebellar white matter and cerebellar atrophy). MRIs were performed in these 13 cases: six had cerebellar white matter lesions, two had cerebellar and brainstem involvement, one had only brainstem alterations, and five cases showed cerebellar atrophy (one case simultaneously had cerebellar white matter and cerebellar athophy and four cases had isolated cerebellar atrophy). JCV-associated CNS diseases were classified upon admission as follows: 1) classic PML: 42 (89%); 2) PML-IRIS: one (2%); and 3) JCV GCN: four (9%). Two patients with classic PML showed worsening of preexisting PML after the initiation of HAART, in the context of a marked increase in CD4+ cell count and HIV plasma viral load below the limit of detection. Thus, three (6%) of our patients had PML-IRIS.

Among the 15 (32%) patients that had nosocomial pneumonia, 13 (87%) died. Nosocomial pneumonia (p = 0.003), previous diagnosis of HIV infection (p = 0.03), and CT imaging showing cerebellar and/or brainstem involvement (p = 0.02) were associated with in-hospital mortality. CD4+ cell count lower than 100 cells/mm^3 showed a trend toward worse outcome (p = 0.06). Overall mortality during hospitalization was 34% (n = 16). Among 11 patients with follow-up in our Outpatient Care Unit, eight (73%) patients were alive one year after the neurologic diagnosis. Among 20 patients without follow-up in our hospital after discharge, we obtained information on 12 cases, and 10 (83%) of them were alive one year after the

neurologic diagnosis. Among patients with available data (n = 39, 83%), overall mortality one year after the neurological diagnosis was 54% (n = 21). Of these, 16 (76%) died during hospitalization.

Discussion

In this study, although infrequent, novel presentations of JCV-associated CNS diseases were observed; nosocomial pneumonia, previous diagnosis of HIV infection, and cerebellar and/or brainsteam involvement were associated with in-hospital mortality; and overall mortality was high.

JCV-associated CNS diseases constitute a spectrum of diseases of which classic PML represent the most frequent and well described clinical presentation, as confirmed in the present study.

In the HAART era, PML-IRIS happens in two settings. The first is when worsening of preexisting PML occurs after the initiation of HAART (paradoxical IRIS). The second setting is when PML and IRIS develop simultaneously (unmasking IRIS).[10] A recent study reported that approximately 33% and 67% of PML-IRIS correspond to paradoxical and unmasking IRIS, respectively.[11] In contrast to reports from developed countries, where unmasking IRIS accounts for up to 19% of PML cases,[12,13] we found only one (2%) case with this presentation. In addition, two (4%) other patients presented paradoxical IRIS. The reasons for these lower frequencies are unknown. However, some potential variables include timing to start HAART, JCV DNA levels in CSF, and/or JCV genotypes.

Du Pasquier et al.[14] have convincingly demonstrated productive JCV infection of cerebellar granule cell neurons in an HIV-infected patient. Afterward, a novel syndrome, distinct from PML, was called JCV granule cell neuronopathy.[15] Classically, patients with this presentation depict ataxia and cerebellar atrophy without white matter lesions in the cerebellum and show granule cell neurons infected by a JCV variant.[16] We and others have recently characterized JCV mutations in CSF of four JCV granule cell neuronopathy patients, including two from Brazil.[17] In the present study, we found 9% of cases with probable JCV granule cell neuronopathy. Nevertheless, a report found frequent infection of cerebellar granule cell neurons by JCV in PML and suggested that these cells may be the initial site of JCV infection in the CNS of HIV-infected patients.[18]

In previous studies, some variables were associated with worse prognosis among HIV-infected patients with PML, including diagnosis before the HAART era, lower CD4+ cell counts, higher plasma HIV-1 RNA levels, lack of HIV clearance in plasma at month three, higher amounts of JCV DNA in CSF at the time of diagnosis, lack of JCV-specific cytotoxic T-lymphocytes, and brainstem involvement.[7,8,10,12,19-22] In our exploratory analysis, we found that cerebellar and/or brainstem involvement and probably low CD4+ cell count were associated with in-hospital mortality. In accordance with these results, a recent study showed shorter survival time in AIDS-related PML patients with initial brainstem involvement, and 1-year probability of survival was 38% in patients with brainstem impairment versus 75% in patients without impairment.[9] Furthermore, lesions affecting the cerebellum tended to be more disabling, precluding independent living.[23]

The level of immunossupression is an important risk factor for developing PML and dying due to this disease. A study found incidence rates of 0.2 and 9.1 cases per 1,000 person-years at risk, respectively, for patients with CD4+ cell counts ≥ 200 versus < 200 cells/mm^3.[22] Another study estimated that 1-year survival was 48% in HIV-infected patients with CD4+ cell count < 200 cells/mm3 at PML diagnosis compared to 67% in those with CD4+ cell count > 200 cells/mm^3.[21]

In addition, similar to other neurologic complications in our setting, nosocomial pneumonia was common among fatal cases.[24] Finally, we found a poorer outcome in patients with previous diagnosis of HIV infection. Probably this fact reflects non-adherence to HAART or drug-resistant HIV. Prior studies identified a higher survival benefit in patients previously naïve to antiretrovirals who started HAART at the time of PML diagnosis. Probably, in naive patients starting HAART after neurological diagnosis, a rapid control of viral replication or the absence of HIV-resistant mutations may induce a more effective control of HIV replication, resulting in a more complete JCV-specific immune recovery.[19]

In developed countries, the survival of patients with PML has increased substantially over the past 10 years, from 0-30% one year after the diagnosis in the pre-HAART era to 38-62% since its introduction.[8,10,12,23] In addition, PML has a three month mortality rate of 20-50%.[8] Thus, the outcome of our patients was similar to that observed in developed countries, suggesting that the natural history of the disease can be modified in developing countries with access to HAART, and that the prompt institution of HAART is the most effective therapeutic approach in order to increase survival, at least in a subset of patients.[24] The overall mortality during hospitalization was high and could be justified, at least in part, due to the long time from the beginning of the symptoms until the diagnosis and subsequent antiretroviral treatment. Most patients included in this study were referred to our center after several evaluations in other services, usually of primary or secondary care and, in some instances, receiving unnecessary and prolonged empiric treatment (for example for cerebral toxoplasmosis).

A recent nationwide cohort study performed in Denmark found that the median survival time among patients with PML diagnosed in the HAART era was 1.8 years.[22] Thus, despite the advances in recent years, the prognosis for patients with PML remains poor. This disease will continue to occur due to several reasons: patients fail to use HAART (not under care or noncompliant with HAART), HAART failure due to resistance, and late HIV diagnosis (late presenters). In this setting, the main focus in the management of PML should be to avoid severe immunodepression in HIV-infected patients.[22]

In conclusion, PML constitutes the most frequent JCV-associated CNS disease in our setting, but novel presentations were observed. Nosocomial pneumonia, previous diagnosis of HIV infection, and cerebellar and/or brainstem involvement were associated with in-hospital mortality. Despite increasing survival of patients with PML in the HAART era, overall mortality continues to be high.

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