ORIGINAL RESEARCH PAPER
Volume-6 | Issue-12 | December-2017 | ISSN No 2277 - 8179 | IF : 4.176 | IC Value : 93.98
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

PROGRESSIVE MULTIFOCAL LEUCOENCEPHALOPATHY (PMLE)

Neurology

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ABSTRACT

Progressive multifocal leukoencephalopathy (PML) is a devastating demyelinating disease with significant morbidity and mortality and no effective, targeted therapies. It is most often observed in association with abnormalities of cell-mediated immunity, in particular human immunodeficiency virus (HIV) infection, but also occurs in association with lymphoproliferative diseases, certain immunosuppressive and immunomodulatory regimens, and other conditions. Unfortunately, no treatments have been convincingly demonstrated to be effective, though some have been employed in desperation; treatment otherwise includes attempts to restore any immune system defect, such as the withdrawal of the causative agent if possible, and general supportive care.

KEYWORDS

PMLE JC Virus Natalizumab HIV

Introduction:

Progressive Multifocal Leukoencephalopathy (PML) is a poten- tially fatal or disabling infection of the brain by the JC virus that almost always occurs in the setting of immunosuppres- sion. In the past three decades, PML has taken on new importance in the era of HIV/AIDS and monoclonal antibodies used in the treatment of multiple sclerosis (MS) and auto- immune conditions, such as rheumatoid arthritis [1]. JC virus induced PML is regarded as an opportunistic infection of the human nervous system. AIDS is the most common associated immunocompromising illness in recent years, but non-AIDS immunosuppressive illnesses also cause PML. In past years, lymphoreticular malignancy, such as chronic lymphocytic leukemia or non-Hodgkin lymphoma, have caused PML. These are considered B-cell neoplasms. The importance of B cells in PML pathogenesis is not yet fully understood, but some researchers have suggested B cells carry JC virus into the brain. Other diseases associated with immunosuppression, such as those related to organ transplantation, and immunosuppression associated with rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus, and dermatomyositis, have all caused PML.

The JC Virus:

PML, first described as a neuropathologic entity in 1958, was noted to be a microscopically multifocal demyelinating disease, with coalescence-forming macroscopic lesions [2]. Histologically, oligodendrocyte nuclear enlargement and bizarre astrocyte formation established the disease as unique. Early on, it was suspected to be a viral illness, based on the pathologic appearance of the inclusion-bearing oligodendrocytes and its occurrence in immunosuppressed populations [3]. At the advent of electron microscopic investigation, electron micrographs revealed polyomavirus-size particles in the nuclei of the infected oligodendrocytes [4].

Although the pathogenesis of JC virus entry into the brain remains somewhat unclear, in 1988 B cells were reported to contain JC virus in patients with PML [5]. Other authors subsequently showed that JC virus was detected in lymphocytes of PML and HIV-positive patients by PCR [6]. The PCR revolution in virology affected the diagnosis of PML. For the first time, in 1992, JC virus was detected in the spinal fluid of patients with PML [7,8]. This has become the noninvasive standard for diagnosing PML and has now become accepted as a surrogate marker for histologic proof of JC virus replication in the brain [9].

PML and the JC virus:

In immunocompetent individuals, the JCV is rarely pathogenic, but in immunocompromised patients, it may cause PML, an aggressive, progressive neurologic syndrome that is potentially devastating. Prior to the availability of highly active antiretroviral therapy (HAART), PML was observed in 5–10% of all persons with AIDS, and HIV/AIDS has been an underlying predisposing cause of PML in more than one-half of individuals [11]. Following the advent of HAART, the incidence of PML in this population has declined [10]. Another cluster of PML cases is observed in patients receiving immunomodulatory therapies. Two therapies in particular appear to predispose to PML, namely natalizumab (trade name Tysabri) and efalizumab (now off the market) [12]. However, PML has been reported with the use of rituximab, belatacept, fingolimod, infliximab, alemtuzumab, mycophenolate mofetil, fludarabine, leflunomide, and fumaric acid esters as well [13]. The increased risk of PML from natalizumab is thought to be due to the known mechanism of the drug, namely $\alpha 4\beta 1$ integrin binding. In so doing, this monoclonal antibody prevents lymphocytes from binding to vascular cell adhesion molecule 1 (VCAM) on the central nervous system (CNS) endothelium, decreasing CNS immune surveillance [14]. While an immune-modulated state is relatively common, PML remains a rare disorder even within these subpopulations. This suggests that immunosuppression alone is insufficient to reactivate the JCV and cause disease.

Pathophysiology:

The etiologic agent, the John Cunningham virus (JCV) is a ubiquitous polyoma virus that exclusively infects humans [15]. The enclosed circular genome is comprised of coding (90% of genome) and regulatory regions (10% of genome) that are encoded counterclock wise and clockwise, respectively. Tissuetropism of the virus is determined largely by the hypervariable non-coding control region (regulatory region) while the genomic regions coding for regulatory and structural proteins are largely conserved [16]. JCV found in the brain of patients with PML is referred to as the "prototype" virus and differs from the ubiquitous "archetype" virus due to insertions, deletions, re-arrangements, and importantly, tandem repeats in the regulatory region of the virus. PML occurs when JCV is unchecked by cellular immunity, reactivates, and migrates to the CNS where it infects glial cells. Neurotropism of JCV is not limited to glial cells as JCV can cause a fulminant JCV encephalopathy of cortical pyramidal neurons [17] and agranule cell neurono- pathy of the cerebellum [18].

PMLE:

The diagnosis of PML requires clinical, radiographic, and virologic evidence [19]. Clinically, PML can present with a wide constellation of neurologic signs and symptoms due to its ability to affect virtually any area of the brain and the frequently multifocal nature of the lesions. In patients with multiple sclerosis (MS) on natalizumab or other disease-modifying drugs that seem to predispose to PML, distinguishing PML from an acute MS attack can be difficult, as the general symptoms can be similar to the symptoms of an MS flare. The most commonly reported symptoms include gait changes, weakness, cognitive impairment, sensory symptoms, headache, and visual changes [20]. Visual symptoms are reported in one-quarter to one-half of all PML

patients, typically presenting as a field deficit, and can be the initial symptom as well [21]. Visual system involvement is secondary to involvement of the visual pathways and not as a direct optic neuritis, as seen in other inflammatory, demyelinating diseases [21].

PML presents clinically as a focal or multifocal neurologic disorder. The disease, progressive multifocal leukoencephalopathy, was named for neuropathologic observation of microscopic multifocal lesions involving the brain white matter [22]. However, clinically, a more typical presentation is of a unifocal syndrome of cerebral or brainstem dysfunction. The frequency of MRI focal versus multifocal abnormalities at the time of clinical presentation differs among various authors. Some regard PML to have typically multifocal changes on MRI, even with unifocal clinical presentation. Others suggest that most patients present with a unifocal MRI scan and clinical unifocal syndrome simultaneously [22]. Whichever is correct, a multifocal or unifocal PML clinical presentation is possible.

The neurologic presentation of PML reflects varying locations of the brain affected. Motor system involvement causes corticospinal tract findings. Cortical sensory loss, ataxic cerebellar deficits, and focal visual field defects are common. "Cortical" deficits, such as aphasia or visual-spatial disorientation, can occur because PML demyelination is often immediately subcortical, undermining the cerebral cortex identified with the clinical syndrome. Most patients with PML without AIDS have neurologic focal deficits from cerebral hemisphere abnormalities. The ratio of cerebral versus brainstem involvement is approximately 10:1. For reasons that are unclear, brainstem involvement happens more commonly in patients with PML who have AIDS, with a cerebral to brainstem ratio of involvement approximat ing 4:1 [23].

On computed tomography (CT) imaging, PML lesions are hypointense within the white matter. When the subcortical arcuate fibers are involved, the lesions can have a 'scalloped' appearance. By MRI, a far more sensitive measure to detect evidence of PML, lesions are hyperintense by T2 and fluid-attenuated inversion recovery (FLAIR) imaging and hypointense by T1. Gadolinium enhancement is more common in natalizumab cases, one-third vs. 15% of HIV-associated cases [20].

Treatment:

No treatments have proven to be effective for PML. General principles about treatment include improvement in immune status. Antiviral therapy may promote survival [24]. Therapies can be offered if the goal of neurologic stabilization satisfies the patient's quality-of-life goals. Although the prognosis of PML is generally dismal, removal of the immunosuppression influence of an external drug allows the patient's own immune system to clear JC virus from the brain. This is an effective approach but can also lead to IRIS, which, when it occurs in the brain after immune restoration, may need treatment. IRIS should be treated if accompanied by neurologic deterioration with short-term corticosteroids. In patients with AIDS, cART should be initiated. If the patient with AIDS is already receiving cART, therapy should be changed to optimize immune restoration and normalization of the CD4 count. Cytosine arabinoside has failed in patients with AIDS-related PML [25]. For deteriorating patients with PML with or without AIDS, cidofovir can be considered, [26] although several studies have suggested it is ineffective [27,28]. PML is an aggressive brain infection caused by the JCV, almost exclusively found in immunosuppressed patients. Although consensus is that high-risk patients on immunosuppressant medications such as natalizumab should be monitored by serial imaging and anti-JCV antibody screening, the frequency of testing and the threshold for concern is a rapidly moving target. The mainstays of treatment include stopping the inciting agent and plasma exchange, although directed anti-viral therapeutics is an active area of investigation. While the duration of therapy with natalizumab influences the risk, many other factors are involved in the development of PML, suggesting a complexity to the predisposition to PML development.

Conclusion:

- In general, PML has been regarded as nearly a universally fatal disease. However, more recent experience with PML suggests that patients can survive.
- A pre- AIDS era study showed the 4-month survival rate to be 30%, and the 12-month survival rate 15%. In the pre-cART era, AIDS-related PML was fatal in 95% of patients in 6 months [29].
- With PML, prognosis and therapy is largely driven by underlying cause. In the HIV positive patient population, CD4+ T cell counts can be associated with survival.

REFERENCES

1. Carruthers RL, Berger J. Progressive multifocal leukoencephalopathy and JC -related disease in modern neurology practice. Multiple Sclerosis and Related Disorders (2014) 3, 419–430.
2. Astrom KE, Mancall EL, Richardson EP Jr. Progressive multifocal leuko-encephalopathy; a hitherto unrecognized complication of chronic lymphatic leukaemia and Hodgkin's disease. Brain 1958;81(1):93Y111.
3. Richardson EP Jr. Progressive multifocal leukoencephalopathy. N Engl J Med 1961;265:815Y823.
4. Zurhein G, Chou SM. Particles resembling papova viruses in human cerebral demyelinating disease. Science 1965;148(3676):1477Y1479.
5. Houff SA, Major EO, Katz DA, et al. Involvement of JC virus-infected mononuclear cells from the bone marrow and spleen in the pathogenesis of progressive multifocal leukoencephalopathy. N Engl J Med 1988;318(5):301Y305.
6. Koralnik IJ. Progressive multifocal leukoencephalopathy revisited: has the disease outgrown its name? Ann Neurol 2006;60(2):162Y173.
7. McGuire D, Barhite S, Hollander H, Miles M. JC virus DNA in cerebrospinal fluid of human immunodeficiency virus-infected patients: predictive value for progressive multifocal leukoencephalopathy. Ann Neurol 1995;37(3):395Y399.
8. Telenti A, Marshall WF, Aksamit AJ, et al. Detection of JC virus by polymerase chain reaction in cerebrospinal fluid from two patients with progressive multifocal leukoencephalopathy. Eur J Clin Microbiol Infect Dis 1992;11(3):253Y254.
9. Ryschkewitsch CF, Jensen PN, Monaco MC, Major EO. JC virus persistence following progressive multifocal leukoencephalopathy in multiple sclerosis patients treated with natalizumab. Ann Neurol 2010;68(3):384Y391.
10. Bozic C, Subramanyam M, Richman S, et al.: Anti-JC virus (JCV) antibody prevalence in the JCV Epidemiology in MS (JEMS) trial. Eur J Neurol. 2014; 21(2): 299–304.
11. Berger JR, Pall L, Lanska D, et al.: Progressive multifocal leukoencephalopathy in patients with HIV infection. J Neurovirol. 1998; 4(1): 59–68.
12. Zaheer F, Berger JR: Treatment-related progressive multifocal leukoencephalopathy: current understanding and future steps. Ther Adv Drug Saf. 2012; 3(5): 227–39.
13. Williamson EM, Berger JR: Infection risk in patients on multiple sclerosis therapeutics. CNS Drugs. 2015; 29(3): 229–44.
14. O'Connor P, Miller D, Riester K, et al.: Relapse rates and enhancing lesions in a phase II trial of natalizumab in multiple sclerosis. Mult Scler. 2005; 11(5): 568–72.
15. Tan CS, Koralnik IJ.Progressive multifocal leukoencephalopathy and other disorders caused by JC virus : clinical features and pathogenesis.Lancet Neurol2010;9:425–37.
16. Jensen PN, Major EO. A classification scheme for human polyoma- virus JCV variants based on the nucleotide sequence of the non coding regulatory region. JNeurovirol2001;7:280–7.
17. Wuthrich C, Dang X, Westmoreland S, McKay J, Maheshwari A, Anderson MP, et al. Fulminant JC virus encephalopathy with productive infection of cortical pyramidal neurons. AnnNeurol 2009;65:742–8.
18. Koralnik IJ, Wuthrich C, Dang X, Rottnek M, Gurtman A, Simpson D, et al. JC virus granule cell neuronopathy: Anovelclinical syndrome distinct from progressive multifocal leukoencephalopathy. AnnNeurol2005;57:576–80.
19. Berger JR, Aksamit AJ, Clifford DB, et al.: PML diagnostic criteria: consensus statement from the AAN Neuroinfectious Disease Section. Neurology. 2013; 80(15): 1430–8.
20. Berger JR: Progressive multifocal leukoencephalopathy. Handb Clin Neurol. 2014; 123: 357–76.
21. Sudhakar P, Bachman DM, Mark AS, et al.: Progressive Multifocal Leukoencephalo pathy: Recent Advances and a Neuro-Ophthalmological Review. J Neuroophthalmol. 2015; 35(3): 296–305.
22. Aksamit AJ Jr. Progressive multifocal leukoencephalopathy: a review of the pathology and pathogenesis. Microsc Res Tech 1995;32(4):302Y311.
23. Aksamit AJ Jr. Progressive Multifocal Leukoencephalopathy. Continuum Lifelong Learning Neurol 2012;18(6):1374–1391.
24. Aksamit AJ. Treatment of non-AIDS progressive multifocal leukoencephalopathy with cytosine arabinoside. J Neurovirol 2001;7(4):386Y390.
25. Hall CD, Dafni U, Simpson D, et al. Failure of cytarabine in progressive multifocal leukoencephalopathy associated with human immunodeficiency virus infection. AIDS Clinical Trials Group 243 Team. N Engl J Med 1998;338(19):1345Y1351.
26. Viallard JF, Lazaro E, Ellie E, et al. Improvement of progressive multifocal leukoencephalopathy after cidofovir therapy in a patient with a destructive polyarthritis. Infection 2007;35(1): 33Y36.
27. De Luca A, Ammassari A, Pezzotti P, et al. Cidofovir in addition to antiretroviral treatment is not effective for AIDS-associated progressive multifocal leukoencephalopathy: a multicohort analysis. AIDS 2008;22(14):1759Y1767.
28. Marra CM, Rajicic N, Barker DE, et al. A pilot study of cidofovir for progressive multifocal leukoencephalopathy in aids. AIDS 2002;16(13):1791Y1797.
29. Du Pasquier RA, Corey S, Margolin DH, et al. Productive infection of cerebellar granule cell neurons by JC virus in an HIV+ individual. Neurology 2003;61(6):775Y782.