Progressive Multifocal Leukoencephalopathy

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Abstract

Progressive multifocal leukoencephalopathy (PML) is a rare, myelin-damaging disease of the central nervous system (CNS) in a setting of immunosuppression that is superimposed by concurrent autoimmune diseases such as multiple sclerosis and AIDS or simultaneous administration of immune modulatory monoclonal antibody drugs such as natalizumab. The causative agent is a Polyomavirus known as John Cunningham (JC) virus (JCV) that affects oligodendrocytes and astrocytes resulting in focal, extensive and progressive demyelination across the brain. The pathogenesis of JCV latent and active infection is yet to be fully understood despite significant medical research. To date, no therapeutic intervention has been very effective in addressing the health implications of PML. In this article, we review the current knowledge on the life cycle of JCV, pathogenesis of PML, highlight important tools in the diagnosis, potential targets for management and therapeutic intervention of PML.

Keywords Progressive multifocal leukoencephalopathy; JC virus; Oligodendrocyte; Astrocyte; Pathogenesis; Latency; Natalizumab

Introduction

Progressive multifocal leukoencephalopathy (PML) is a rare, myelin-damaging disease of the central nervous system (CNS) caused by infection of oligodendrocytes and astrocytes by a Polyomavirus known as John Cunningham (JC) virus (JCV), whose name was taken after the first patient in which the virus was first isolated [1]. The virus belongs to the family of polyomaviridae [1-4]. Its genomic constituent is small, circular, and double-stranded DNA molecule of approximately 5,100 base pairs that is divided into two protein coding regions (early and late) on opposite side of the non-coding control region (NCCR). The NCCR controls the enhancer and promoter regions of the coding element as well as the center of viral replication [5-7].

This opportunistic pathogen is wide-spread among human population and may or may not be accompanied with inflammatory changes. The primary target of PML is an immunosuppressed individual, inherently in association with autoimmune diseases such as multiple sclerosis and AIDS, inflammatory diseases including rheumatoid arthritis, systemic lupus erythematosus and sarcoidosis and or as a side effect of a disease modifying treatment such as monoclonal antibody therapy or cytotoxic drugs [8-11]. A common denominator in all the cases of PML is that the patient's immune system is compromised indicating lack of immunosurveillance.

Pathophysiology of progressive multifocal leukoencephalopathy

The viral agent implicated in this autoimmune disorder has been described over eight decades ago with subsequent identification of the viral particle in intranuclear inclusion bodies of myelin forming oligodendrocytes [12,13] and its isolation from human brain suffering from PML [1]. The disease is associated with a long standing asymptomatic state of latency [1]. It affects many organ systems in the body including the tonsil, kidneys and CNS with a long period of latent inactive infection despite significant antibody seropositivity in the target population. Despite a high prevalence of up to 90% seropositivity, fulminant active infection is considerably very low [14,15]. This suggests that seropositivity does not portend active infection however, an immune compromised individual is at a very high risk of coming down with the infection. PML is been associated with numerous autoimmune and inflammatory diseases such as multiple sclerosis (MS) [9], acquired immune deficiency syndrome (AIDS) [16-21], lymphocytic leukemia [22], or during organ transplant co-administration of immunosuppressant drugs. Recent reports suggesting that immune modulation played critical role in the activation of JCV have attracted a lot of attention [3,9,11,23]. The hypothesis is reinforced by the resurgence of active PML in patients that are undergoing immunomodulatory therapeutic intervention [23,24]. Many of these reports of active PML have been linked to a reactivation of a supposedly "quiescent" JC virus by monotherapeutic or combination immunoregulatory therapy using monoclonal antibodies such as natalizumab, efalizumab, and rituximab [3].

Pathogenesis of progressive multifocal leukoencephalopathy

The life cycle of JCV is illustrated in Figure 1. The first step in tackling the scourge of PML is to have an indebt understanding of the mechanism of disease pathogenesis. PML infection is thought to occur early in the life of an individual and it is mostly likely transmitted through the natural external orifices of the gastrointestinal and respiratory tracts [25-27]. Subsequently, the virus invades local lymphoid tissue and infect the lymphocytes through which other parts of the body such as bone marrow and kidneys become infected and
remain is these sites for a period of latency prior to setting up an active infection in an immune deficient subject [28,29]. It is highly possible that JC virus may have been carried to the brain by B lymphocytes carrier where they remain in a period of latency pending reactivation of the virus due to immunosuppression and lack of immune control. A period of latent infection occurs which is followed by active viremia and lodgement of the virus in various tissues of the body including the kidneys [30], tonsils, [28,31] and brain [32-34] as well as in white blood cells [35,36].

Active progressive multifocal leukoencephalopathy

The mechanism of activation of latent PML infection is unclear and requires more investigation to unravel the order of events that leads to activation of latent infection. It has been observed that HIV-1 transactivator protein Tat is a positive effector of transcription and replication process of PML. This observation offers some explanation on the concomitant increase in active PML infection in AIDS patients [48,49]. In a setting of immune deficiency and lack on immune surveillance, increased viral multiplication that subsequently results into increased viral load will promote dissemination of the viral particle and formation of lesions associated with PML. Further, depressed immune system is incapable of fighting infection and clearance of the viral particle because of lack of cells that are involved in immunosurveillance such the cytotoxic CD8 T cells whose role of fighting and eradicating infection is impaired [50]. Immune modulation by monoclonal antibody therapeutic agents prevents translocation of T lymphocyte through the BBB. This eventually reduces T cell-linked immunosurveillance in the brain that result in the promotion of downstream activation of latent PML infection in the brain [51].

Lesion location and clinical characteristics of progressive multifocal leukoencephalopathy

Like most demyelinating diseases of the CNS that affect oligodendrocytes and to some extent astrocytes such as multiple sclerosis, PML exhibit multiple symptoms, affecting several organs and systems of the body that receive neural input from the brain and therefore the clinical picture is non-specific. The clinical manifestation and neurological impairment in PML are dependent on demyelination, location, size and distribution of PML plaques in the brain. Lesions could be focal, more generalized and observed throughout the brain including the cerebral and cerebellar hemispheres as well as the brain stem [52]. Demyelinated plaques are sometimes confluent, bilateral, and asymmetrical and may be localized in both the gray and subcortical white matter as seen in MRI [53]. Involvement of the cerebral subcortical and periventricular white matter may interfere with motor function implicating pyramidal and or extrapyramidal motor control centers, gait ataxia, altered mental status, speech disorders, sensory and visual impairment [54-56]. All regions of the cerebral hemisphere are potential targets of attack by this virus; however the frontal, parietal and occipital lobes are most frequently affected [57]. Accompanying seizure is suggestive of gray matter involvement [56,58]. The deep gray matter of the cerebrum and the brainstem are not spared by JC virus. Lesions are distributed in the basal nuclei, thalamus and pontine gray and white matter [59,60]. PML lesion localization in the cerebellum is inevitably expressed as cerebellar syndrome [61-63]. Sometimes meningitis and meningoencephalitis have been associated with JCV infection suggesting that this viral particle play some role in promoting inflammatory changes in the brain [64,65]. When inflammation is involved especially during the degradation of myelin sheaths, inflammatory cells such as macrophages are recruited to clean-up by-products of myelin breakdown [66].

Diagnosis of progressive multifocal leukoencephalopathy

A combination of clinical signs, laboratory tests, histopathological findings and diagnostic imaging techniques are employed to arrive at a definitive diagnosis of PML. Detection and identification of JC viral particle, protein and or DNA fragments in brain tissue samples and or

Figure 1: Life cycle and cellular events in JCV infection indicated by numbers accordingly. 1: free JCV binding to carbohydrate [C₉₋₉(H₂O)₉] receptor coupled serotonin (5HT2A) receptors on cell surface, 2: phagocytosis of viral particle, 3: transcytosis and formation of endosome, 4: internalization into endoplasmic reticulum (ER), 5: cytoplasmic translocation from ER, 6: nuclear internalization via nuclear pores for exshainment and nuclear processing, 7: transcription of early viral coding region, 8: translation of early mRNAs, 9: nuclear relocaction, 10: replication of viral particle, 11: transcription late viral coding region, 12: translation of late viral transcript, 13: nuclear localization of capsids, 14: final nuclear packaging, 15: intracellular release of viral particles, 16: extracellular release of free JCV viral progeny ready to infect other cells.

Among the neuroglia, oligodendrocytes and astrocytes are the main targets of JC virus whose infection results in severe demyelination and inflammation marked by infiltration with macrophages [32,37-40]. Following JCV binding to cellular surface sialic acid-linked carbohydrate receptor [C₉₋₉(H₂O)₉] coupled serotonin (5HT2A) receptors, the viral particles become internalized by endocytosis (Figure 1). Endosome is formed, mediate by a vesicular capsid protein, clathrin, for onward translocation into the nucleus [45,46] via the endoplasmic reticulum (ER) [47]. In the nucleus, the viral particle undergoes DNA replication, transcription and encapsulation [38,39] and subsequently released as free active progeny virions with the potential to infect many more cells. Sequel to the release of the viral particle, the infected neuroglia undergoes necroses that is accompanied by the infection of adjacent glial cells in progression and terminally result in precipitation of PML.
in vivo

Therapeutic intervention in progressive multifocal leukoencephalopathy

To date, there is relatively no effective treatment for PML. Many therapeutic agents have been used to mitigate the health effects of PML with variable or no significant beneficial effects and sometimes the adverse effects of the drug dominate [68]. Several therapeutic targets have been suggested taking into account the life cycle of JCV and the pathogenesis of PML (Figure 1) [53], but attempts to harness the high points of these targets for treatment intervention have not been clinically very successful in vivo [68,69]. The objective of any therapeutic intervention is to disrupt the life cycle of JCV virus from the time of infection of the cell through intracellular transformation to the release of newly formed active viral progeny (Figure 1) [53]. These may include inhibition of viral-surface receptor interaction and internalization, DNA replication, transcriptional, and translational processes [53].

Serotonin (5HT2A) receptor antagonist, Mefloquine, a substrate of the P-glycoprotein transporter and antimarial medication inhibits JC viral adsorption, phagocytosis into the cell, and viral DNA replication. It showed some promise against JCV in vitro [70], but the in vivo result was variable [71]. The same is true of Mefloquine analogue and a serotonin receptor blocker, mirtazapine [72]. The clinical trial with cytarabine (cytosine arabinoside), a Viral DNA synthesis inhibitor, failed to show any clinical benefit in PML patients [73-75] however some studies showed positive results [76-78]. The result of interleukin-2 clinical trial was quite variable and unconvincing [79,80]. Similarly, treatment with beta-interferon, an inhibitor of viral replication, yielded variable results [81,82]. The effect of cidofovir, an antiviral drug and inhibitor of viral replication on PML was variable [83,84]. Further, clathrin-mediated endocytosis [38] inhibitor, chlorpromazine, acting singly or in combination with clozapine showed some prospect on glial cell culture in vitro [85] but it was of little or no benefit in clinical trial in vivo [69]. So far, there is no treatment intervention that is effective in addressing the health effects of PML. The objective of any therapeutic intervention in PML is to improve and maintain a very healthy immune system that will promote immune surveillance and prevent immunosuppression. The hypothesis is reinforced by the beneficial effect of IL-2 administration that restored the immune status and improves the level of CD4+ count [79].

Conclusion

Several predictions and unanswered questions abound in the pathogenesis of PML with respect to mode of transmission, internal localization of the latent infection, mechanism of reactivation of the rather "quiescent" viral particles, dissemination and establishment of lesions pathognomonic to PML as well as available treatment options that will be beneficial for PML patients. Clearly, any attempts to address these questions would require more research.

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Conflict of Interest

The authors declare that they have no financial or other conflicts of interest in relation to this review article and its publication.

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