7-2016

Progressive Multifocal Leukoencephalopathy in Multiple Sclerosis

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Introduction

Progressive multifocal leukoencephalopathy (PML) is a rare and debilitating disease caused by the JC virus and results in demyelination of oligodendrocytes and glial cell lysis, leading to plaque development on the brain and neurological problems (Gorelik et al., 2011). PML develops in individuals who have an immune disorder and who have been treated with immunomodulatory medications. Such individuals include those affected with Multiple Sclerosis (MS) (Gorelik et al., 2011). MS is a disease that involves inflammation of the central nervous system and causes a progressive decline in neurological function and is believed to be a result of self-antigens and an autoimmune response (Keating & McCormack, 2014). There is no cure for MS and the majority of cases are classified as relapse-remitting (Major & Douek, 2013).

The first-line medications used to treat MS show only a 30% reduction in relapses per year. Recently a new medication, Natalizumab, has shown a 68% reduction in relapses per year (Baldwin & Hogg, 2013). While Natalizumab shows promise in the treatment of MS, the drug has shown to increase the risk of development of PML, especially in long-term use (more than 18 months) (Schwab et al., 2013). There is no cure for PML and 30-50% of patients who develop the disease die within the first few months of diagnosis. Those that survive, are typically left with severe neurological damage (National Institute of Neurological Disorders and Stroke [NINDS], 2015).

As an Advanced Nurse Practitioner (ANP), the author will encounter patients diagnosed with MS, as MS is a fairly common neurological disorder with 1 in 750 people in the United States at risk for developing the disease (National Multiple Sclerosis Society, n.d.). These patients may be newly diagnosed or looking for new treatment options. Knowing the risk of PLM, signs and symptoms and its effects can assist the ANP and the patient in making an informed decision about their treatment options.

Signs and Symptoms

- Signs and symptoms of PML can vary greatly depending on the area of the brain that is affected (Berger et al., 2013).
- Patients may initially present with distinct behavioral or cognitive changes that are reported by family members (Fitzgerald, 2015).
- Other neurological symptoms that can occur include hemiplegia, lethargy, aphasia, anxiety, fatigue, seizures, impaired memory and ataxia (Fine, Sorbello, Kortepeter, & Scarazzini, 2014).
- The disease continues to progress slowly over time with worsening symptoms, leading to death or neurological disabilities (NINDS, 2015). See Figure 1.

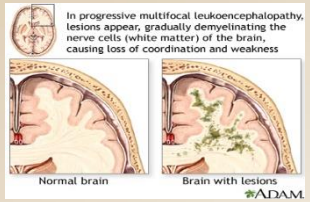

Figure 1 retrieved from:
http://nethealthbook.com/articles/progressive multifocalleukoencephalopathy.php

Underlying Pathophysiology

- PML is thought to be caused by the JC virus. The JC virus was discovered after virions were observed on the bodies of oligodendrocytes. Although much has been learned about the virus, there is still a lot that needs to be discovered to gain a better understanding of the JC virus and PML (White & Khalili, 2011).
- The JC virus is thought to affect 66-92% of the general population, as evidence by JC antibody prevalence in populations studied, and is acquired in childhood (White & Khalili, 2011). Despite the prevalence of JC antibodies, the actual occurrence of PML is low leading to the conclusion that the virus is re-activated, after a period of latency, in immunosuppressed individuals (White & Khalili, 2011).
- The JC virus is transmitted during childhood and is thought to have initial portal of entries into the tonsils and GI tract. The body's immune system fights the virus, defeats the virus, and then the virus enters a latent stage within the tonsils, bone and/or kidneys. The majority of people infected with the latent JC virus will never know the virus is there, unless they develop an autoimmune disorder or take immunosuppressive medications (White & Khalili, 2011). See Figure 2.
- The latent form of the JC virus can also be found in the bloodstream, particularly in B lymphocytes and can circulate in the brain (White & Khalili, 2011).
- Cytokines are released due to the autoimmune response in MS, causing a reactivation of the JC viral transcription and replication. A PML lesion on the brain can then develop due to the initial immunosuppression (White & Khalili, 2011).
- CD8 T cells play an important role in eliminating viruses and controlling their spread. Natalizumab suppresses T lymphocytes from crossing the blood-brain barrier, in an effort to control the demyelination in MS, which may prevent these cells from suppressing the latent JC virus adding to the reactivation and development of PML (White & Khalili, 2011).
- The resulting development of PML plaques can lead to glial cell lysis and demyelination leading to neurological signs and symptoms (White & Khalili, 2011).

Significance of Pathophysiology

- The pathophysiology is significant in that many patients diagnosed with MS and attempting or undergoing immunosuppression therapy may also have the antibodies for the JC virus which increases their risk of reactivating the infection, resulting in PML. Therefore, screening and close observation is warranted in the patient with MS.
- The pathophysiology of the disease assists in diagnosing. The lesions that develop in the white matter of the brain can often be observed on MRI (see Figure 3), the signs and symptoms come on gradually as the disease spreads throughout the brain, and cerebral spinal fluid can be analyzed for presence of the JC virus or antibodies (Berger et al., 2013).
- Patients with MS that had prior immunosuppression therapy or another underlying immune disorder, develop PML at a rate of 13 to 1,000. The statistics are significant and warrant antibody testing and diligent surveillance for the JC virus and PML with attempted or long-term use of natalizumab (Susman, 2015).

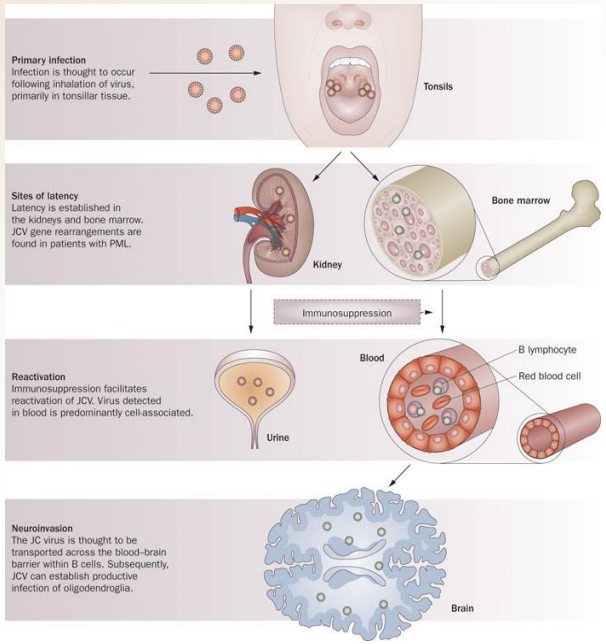

Figure 2 retrieved from:
http://www.nature.com/nrneurol/journal/v6/n12/fig_tab/nrneurol.2010.164_F1.html

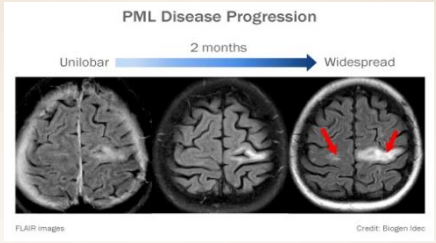

Figure 3 retrieved from:
http://pmlconsortium.org/healthcare-professionals/diagnosis

Implications to Nursing Care

- The APN should be aware that any patient presenting with a history of MS and taking natalizumab, can begin showing signs of PML at any time, particularly after long-term therapy. The APN should also be aware that when a patient with a history of MS presents with new symptoms, there is a chance that the symptoms may not be a result of MS, but of PML and quick action is needed (Fitzgerald, 2015).
- Symptoms of MS relapse tends to develop quickly, over hours to days while PML symptoms occur more slowly (Fitzgerald, 2015).
- MS responds to steroid therapy or levels off, whereas PML continues to progress despite treatment (Fitzgerald, 2015).
- Most patients with MS are cared for by a specialist, however APNs may encounter these patients in family practice or even in the acute care setting and need to be aware of PML and its effects. Symptom management and attempting to improve quality of life may be a vital part of the APN's role when dealing with a patient with PML.
- APNs in family practice may encounter newly diagnosed patients with MS and needs to be able to discuss the treatment options and risks/benefits to assist their client during that difficult time. Therefore, an understanding of PML and its relation to MS is important.

Conclusion

The JC virus is a fairly common virus that many people are unaware they have been infected with and usually remains dormant for life. However, the virus can be reactivated in certain immunosuppressive conditions, as in MS and certain medications for its treatment, causing the development of PML (Gorelik et al., 2011). PML affects glial cells and creates lesions/plaques on the brain that can cause severe neurological disabilities and lead to death. There is no cure for the disease and treatment focuses on symptom management and attempting to slow the progression with plasma exchange (NINDS, 2015). A combination of MRI to look for PML associated lesions, cerebrospinal fluid analysis for antibodies and signs and symptoms lead to the diagnosis of PML (Fitzgerald, 2015). The APN should be aware that PML can develop in patients with MS and know what signs to look for and when further testing is needed. If PML is suspected, fast action and referral is needed by the APN.

References

Baldwin, K.J. & Hogg, J.P. (2013). Progressive multifocal leukoencephalopathy in patients with multiple sclerosis. *Current Opinion Neurology, 26*(3), 318-323. doi: 10.1097/WCO.0b013e328360279f

Berger, J.R., Aksamit, A.J., Clifford, D.B., Davis, L., Koralnik, I.J., Sejvar, J.J.,...Nath, A. (2013). PML diagnostic criteria. *Neurology, 80*(15), 1430-1438.

Fine, A.J., Sorbello, A., Kortepeter, C., & Scarazzini, L. (2014). Progressive multifocal leukoencephalopathy after natalizumab discontinuation. *Annals of Neurology, 75*(1), 108-115.

Fitzgerald, S. (2015). Third plm case associated with fingolimod: how to distinguish pml from ms relapse. *Neurology Today, 15*(19), 10-11.

Gorelik, L., Reid, C., Testa, M., Brickelmaier, M., Bossolasco, S., Pazzi, A.,...Cinque, P. (2011). Progressive multifocal leukoencephalopathy (PML) development is associated with mutations in JC virus capsid protein VP1 that change its receptor specificity. *The Journal of Infectious Diseases, 204*(1), 103-114.

Keating, G.M., & McCormack, P.L. (2014). Natalizumab: a guide to its use in relapsing-remitting multiple sclerosis. *Drugs and Therapy Perspectives, 30*(2), 48-54.

Major, E.O., & Douek, D.C. (2013). Risk factors for rare disease can be risky to define: pml and natalizumab. *Neurology, 81*(10), 858-859.

National Institute of Neurological Disorders and Stroke. (2015). NINDS progressive multifocal leukoencephalopathy information page. Retrieved from http://www.ninds.nih.gov/disorders/pml/pml.htm

National Multiple Sclerosis Society. (n.d.). Who gets MS? (Epidemiology). Retrieved from http://www.nationalmssociety.org

Schwab, N., Schneider-Hohendorf, T., Posevitz, V., Breuer, J., Gobel, K., Windhagen, S.,...Wiendl, H. (2013). L-selectin is a possible biomarker for individual pml risk in natalizumab-treated ms patients. *Neurology, 81*(10), 865-871.

Susman, E. (2015). Two new studies on natalizumab: Is extending the time between doses safe? Can dosing be stopped during pregnancy? *Neurology Today, 15*(21), 18-24.

White, M.K., & Khalili, K. (2011). Pathogenesis of progressive multifocal leukoencephalopathy-revisited. *The Journal of Infectious Diseases, 203*(5), 578-586. doi: 10.1093/infdis/jiq097

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