Summer 7-28-2019

Multiple Sclerosis Pathophysiology

Carolyn Ricketts
ricketts1@otterbein.edu

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Carolyn M. Ricketts, BSN, RN-C
Otterbein University, Westerville, Ohio

Introduction

Neurologic diseases are often difficult to comprehend since the Neurosystem is very complex. Multiple Sclerosis (MS) is among one of the many neurologic diseases in which there is no cure and it is unknown why exactly it develops. According to Khorramdelazad, H., Bagheri, V., Hassanshahi, G., Zeinali, M., & Vakilian, A. (2016), MS "is the main cause of nontraumatic neurological disability in young adults" (p. 72). MS is a chronic autoimmune inflammatory disease resulting from inflammation of the central nervous system (CNS), blood-brain-barrier (BBB) breakdown, and demyelination of the brain and spinal cord white matter leading to lesions and axonal damage affecting the CNS (Guan, Y., Jakimovski, D., Ramanathan, M., Weinstock-Guttman, B., & Zivadinov, R., 2019). This damage is followed by complete or partial recovery with scaring or sclerosis (McCance, K. L., & Huether, S. E. (eds.)., 2018). Family Nurse Practitioners (FNP) and other healthcare professionals need to understand and assist with early treatment as well as manage lifelong treatment for the MS patient to maintain or improve quality of life.

Risk Factors

- Greatest risk: Infectious mononucleosis during early adulthood
- Exposure to the Epson-Barr virus (EBV) (present in 90% of the general population, 30-40% of those will develop infectious mononucleosis) Reactivation of EBV has a positive correlation with relapses
- Smoking ⟶ Worse disease progression & worse MRI outcomes
- Vitamin D deficiency ⟶ hypothesized to increase risk of developing MS, causing worse outcomes & higher occurrence of relapses
- MS occurs in higher rates in areas further from the equator

(Guan et al, 2019).

- The gut microbiome & dietary patterns
- Genetic susceptibility

(Grigoriadisa, N., & Van Pesch, V., 2015)

- **The Hygiene Hypothesis:** Areas with better hygiene & sanitation result in youth exposed to less pathogens leading to higher rates of autoimmune diseases (Guan et al, 2019).

Signs & Symptoms

- Onset between 20-40 years; life expectancy not greatly altered
- More common in females
- Males may have more severe progressive course
- First demyelinating event: commonly a single neurologic dysfunction lasting longer than 24 hours without fever, infection, or encephalopathy.
- *Multifocal:* Paresthesia of the face, trunk, or limbs, weakness, impaired gait, visual disturbances, urinary incontinence, optic neuritis most commonly in one eye with progressive blurring & pain
- *Spinal cord syndrome:* in sensory or motor tracks starting on one side of the body & progressing to the other,
- *Brainstem syndromes:* facial sensory loss or weakness, vertigo, or double vision.
- *Cerebellar syndromes*: lack of coordination, tremor, gait instability, ataxia.
- *Cerebrum symptoms:* hemifacial weakness, pain, motor impairments.
- *Cognitive impairments:* occur later in disease: memory & attention problems as well as Psychiatric disorders, depression, dementia

(McCance, K. L., & Huether, S. E. (eds.)., 2018).

- Characterized by flare-ups or attacks of symptoms that can last from days to weeks. Can either resolve or become permanent (Khorramdelazad et al, 2016).
- 70% of MS patients experience cognitive impairment from mild forgetfulness to mild to moderate dementia (Maloni, H., 2018)

Underlying Pathophysiology

- "A diffuse and progressive CNS inflammatory autoimmune disease that affects white and gray matter" anywhere in the CNS (McCance, K. L., & Huether, S. E. (eds.)., 2018, p. 581).
- Adaptive & innate immunity involved ⟶ inflammation from oxidative injury & mitochondrial dysfunction from oxidative free radicals in microglia & macrophages. Oxidative injury amplified with aging by microglia activation, progressive mitochondrial damage, & accumulation of iron in the CNS (Grigoriadisa, N., & Van Pesch, V., 2015).
- B cells, T cells, & macrophages breech BBB of the brain & spinal cord, "recognize myelin autoantigens and produce myelin-specific antibodies triggering inflammatory demyelination" (McCance, K. L., & Huether, S. E. (eds.)., 2018, p. 581).
- Leads to loss of oligodendrocytes & myelin sheaths ⟶ disrupt nerve connections (McCance, K. L., & Huether, S. E. (eds.)., 2018).
- TH1 & TH17 pro-inflammatory lymphocytes activated in periphery, cross the BBB, penetrate the CNS & are reactivated by CNS antigens inducing an inflammatory response inducing macrophage & microglial activation creating more pro-inflammatory mediators, oxygen, & nitric oxide radicals causing demyelination & axonal loss (Grigoriadisa, N., & Van Pesch, V., 2015).
- Relative preservation of axons & glial or astrocytic scar formation
- Relapse = at least partial repair
- Progressive forms can lead to death of neurons and brain atrophy

(McCance, K. L., & Huether, S. E. (eds.)., 2018

Epson-Barr Virus and the Two-Hit Hypothesis Pathophysiology of MS:

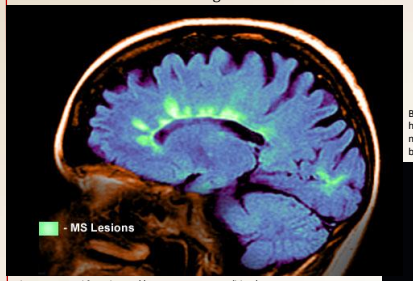
- Memory B cells (antigen presenting cells) act as reservoirs for EBV & are thought to enhance BBB permeability allowing pre-existing polyclonal antibody-producing B cells to enter the CNS
- Memory B cells activate auto-aggressive T-cells against myelin proteins
- High levels of CD40 on B cells suggest a higher level of antigen presentation of EBV; associated with higher levels of neurodegeneration & found in actively demyelinating lesions
- EBV immortalizes Memory B cells interacting with tumor suppressor genes ⟶ become undetectable to T-cell surveillance

(Guan et al, 2019).

- Acute axonal damage has been correlated with CD8+ T cells, pro-inflammatory mediators with cytologic activity against EBV, found in the brain & cerebral spinal fluid (Grigoriadisa, N., & Van Pesch, V., 2015)

Multiple Sclerosis Case

A 24-year-old Caucasian female visits a Columbus, Ohio clinic with complaints of blurry vision in her right eye that started two days ago. She states she is tired all the time and has been having "weird things" occurring to her for the past several years, such as the inability to concentrate, trouble following simple instructions at times, sharp pains shooting through her right arm at random, and being unstable on her feet occasionally. Her symptoms have always resolved and she states she "always contributed it to stress."
She has a history of infectious mononucleosis as a teenager.
Physical examination reveals right-hand grasp is slightly weaker than left, nystagmus of the right eye, and some pain with eye movement.
She is afebrile, vital signs are normal, no findings of any infection
She is referred to a neurologist and a brain MRI is ordered, which reveals a diagnosis of MS



Above retrieved from https://www.amsvans.com/blog/wp-content/uploads/2012/06/mri-scan-showing-ms-lesions.jpg

Below retrieved from https://images.fineartamerica.com/images-medium-large/5-mri-of-multiple-sclerosis-medical-body-scans.jpg

MRI is the most sensitive tool to diagnose & monitor MS (Guan et al, 2019). These photos are MRIs of patients with MS. Macrophages & microglial cells have been found in active MS lesions" (McCance, K. L., & Huether, S. E. (eds.)., 2018).

Symptom subtype of MS	Symptoms	Area of Impact
Relapsing-Remitting *Most common*	Recurring exacerbations of previous symptoms with acute axonal loss followed by complete or partial recovery that lasts days to months (Guan et al, 2019).	Dominated by multifocal inflammatory demyelinated plaques in white matter (Grigoriadisa, N., & Van Pesch, V., 2015).
Primary Progressive *Least Common*	Gradual progression & continuously accumulating physical disability without relapse (Guan et al, 2019).	Most prevalent in the spinal cord with gradual loss of power in lower limbs, asymmetric, bowel & bladder problems (McCance, K. L., & Huether, S. E. (eds.)., 2018).
Secondary Progressive	• Relapsing-remitting evolve into progressive disease with worsening disability with or without relapses (Guan et al, 2019 • Relapses get shorter in duration & symptoms progressively more severe (McCance, K. L., & Huether, S. E. (eds.)., 2018).	Inflammation compartmentalized in the CNS "characterized by the presence of ectopic lymphoid follicles particularly in the meninges" (Grigoriadisa, N., & Van Pesch, V., 2015, p.8).
Progressive Relapsing	"Steadily worsening symptoms from the onset with clear acute relapses but often with more severe symptoms" (McCance, K. L., & Huether, S. E. (eds.)., 2018, p. 582).	

Pathophysiology Continued

Human CXCL12 gene and cytokine:

- may be responsible for causing inflammation, remyelination, & neuroprotection
- Facilitate leukocyte recruitment & migration into the CNS
- Important for developmental processes such as hematopoiesis, cardiogenesis, vascular formation, neurogenesis
- Alterations in CXCL12 gene expression, located on chromosome 10, recruits & facilitates CXCR4-expressing mononuclear cells across BBB leading to progression & development of MS
- Active and silent lesions have CXCL12 present

(Khorramdelazad et al, 2016).

- Axonal transection & damage: Linked to brain atrophy in MS at a rate of 0.5-1% per year correlates with physical & cognitive disability (Grigoriadisa, N., & Van Pesch, V., 2015)

Significance of Pathophysiology

Early diagnosis & initiation of treatment is important!

- Get inflammation under control to decrease the amount of damage, preventing permanent disability
- Discovering the exact pathology of MS will assist in new treatments & maybe someday a cure
- Main therapies are focusing on antigen presentation, peripheral immune response, the BBB, & target tissue in the CNS

(Grigoriadisa, N., & Van Pesch, V., 2015)

- CXCR4 & CXCL12 currently being researched as a therapeutic target for several systematic autoimmune & neuroinflammatory diseases, such as MS. Serum levels of CXCL12 have potential to be used as a MS prognosis biomarker. Increased levels may correlate with increased levels of autoimmunity

(Khorramdelazad et al, 2016)

- Research for EBV vaccination, not successful currently (Guan et al, 2019).

Nursing Implications

Family nurse practitioners (FNP) in northern United States may encounter MS often (Guan et al, 2019).
MS patients need a well-coordinated team of professionals with shared decision making to diagnose and treat symptoms of MS successfully and improve or maintain quality of life.
FNP role is important in assisting with diagnosis & life-time management:

- Screen for & manage symptoms
- Ask the right questions to discover compensatory behavior & strategize with the patient on ways to improve quality of life:
  - Everyday life ?s: problems with driving, cooking, following a recipe, participating in a group activity.
- Look at underlying conditions that could be causing cognitive impairment
- The Symbol Digit Modalities Test = quick, cost-effective screening for cognitive impairment
- Symptom treatment, interpret lab results, communicate diagnosis, referrals for cognitive rehabilitation & neurologists
- Assist with disability at work & home: cool environment, ergonomic seating, handicap parking, compensatory techniques: recording, planning, use of smart phone apps & reminders, removing distractions, rest, & restorative therapies
- Counsel & advocate for patients & families
- Educate on wellness behaviors: diet high in fruits & vegetables & low in meats, taking antioxidants, vitamin D importance, lifestyle factors, & exercise

(Maloni, H., 2018).

- Educate MS patients on disease modifying therapies (DMT); several available making options complex.
- FNPs teach & be sure patients understand short & long-term side effects, treatment guidelines, & treatment monitoring to maximize success.
- Set realistic expectations, MS is not curable, treatments intended to slow disease progression & limit disease activity.
- FNPs monitor & manage side effects of DMTs

(Roman, C., & Menning, K, 2017)

Conclusion

Multiple sclerosis is a debilitating autoimmune disease characterized by inflammation, demyelination, and damage to nerves with or without relapse. The exact pathology is unknown, but many theories include cells of the innate and adaptive immune system crossing over the BBB and initiating damaging inflammation. Infection by EBV and alteration of the CXCL12 gene are two theories in the pathophysiology and development of MS. The pathophysiology is important for the development of new treatments, possible vaccination, and a possible cure someday. The FNP has an important role of screening patients, making referrals to correct medical providers, educating and advocating for the patient, and monitoring and managing symptoms throughout the MS patients life.

References

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