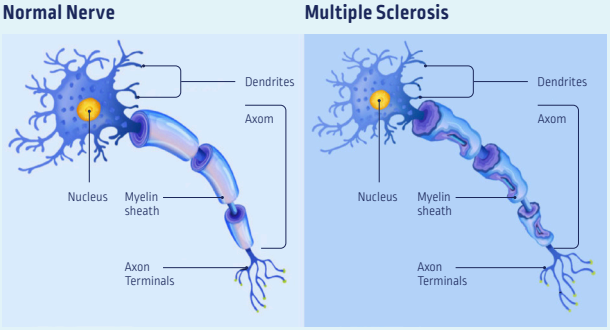
NEXT BIOSCIENCES

Netcells Stem Cells

Central Nervous System Disorders: Multiple Sclerosis

Multiple Sclerosis (MS) is an autoimmune disease where the immune system inappropriately attacks and destroys myelin and oligodendrocytes causing demyelination of neurons in the central nervous system. Myelin is the protective sheath that surrounds the axon of neurons allowing the efficient transmission of electrical impulses and is produced by oligodendrocytes. Currently, MS effects approximately 2.3 million people globally.

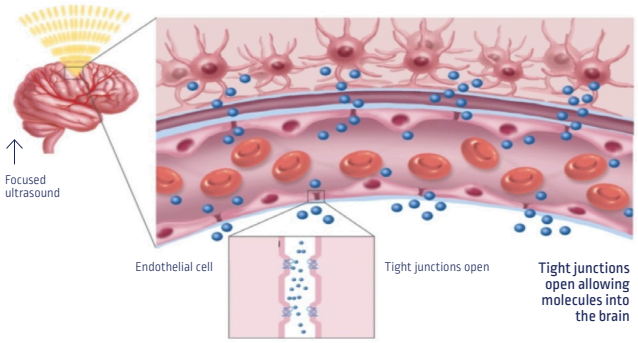


Reference 1

Pathophysiology

The brain and spinal cord are protected from substances in the blood by the blood-brain barrier (BBB) which only lets certain molecules and cells from the blood pass through. Immune cells, like T and B cells, require the correct ligand (surface molecule) to get through the BBB. In MS, there is a massive infiltration of auto-reactive T cells, B cells and antigen-presenting cells, including monocytes and macrophages.

Once a T cell is through the BBB, it can be activated by the unfamiliar environment of the CNS where immune cells do not usually exist. In the case of MS, this is activated by myelin. Once activated, the T cell alters the BBB cells, leading to the expression of more receptors, which allow other immune cells to more easily bind and pass through the BBB.



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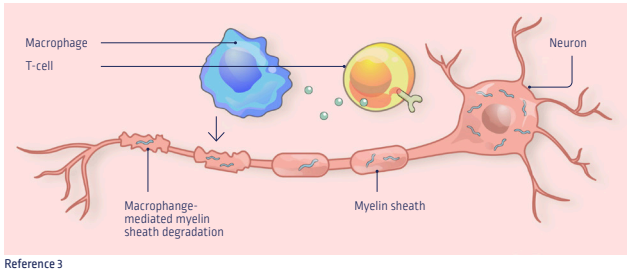
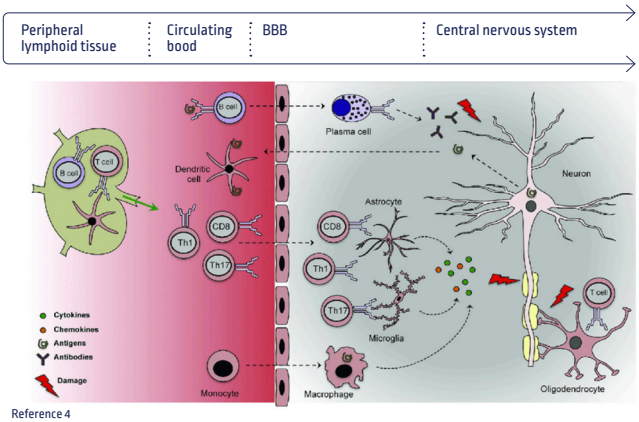


Reference 3

This injury to the BBB and hyperactivation of brain microglial cells leads to a massive infiltration of T and B cells, resulting in a Type IV Hypersensitivity Reaction or cell-mediated hypersensitivity:



Reference 4

The above image describes this type of hypersensitivity. With the influx of T and B cells, the following chain of events occurs:

- Myelin-specific T cells release cytokines such as; IL-1, IL-6, TNF alpha, INF gamma. These cytokines:
  - Dilate the blood vessels of the BBB allowing more immune cells to pass through and cause direct damage to oligodendrocytes.
  - Damage myelin and oligodendrocytes.
  - Attract B-cells and macrophages as part of the inflammatory reaction.

B-cells produce antibodies which mark the myelin sheath proteins, and the macrophages use these antibody markers to engulf and destroy the myelin and oligodendrocytes, leaving scar tissue called plaques or sclera behind.

Overall, these clusters of immune cells cause neuroinflammation in selected parts of the brain.

The immune-mediated attacks occur in bouts, whereby an autoimmune attack on oligodendrocytes is followed by a reduction in inflammation by regulatory T cells.

In the early phases of MS, oligodendrocytes heal and extend out new myelin to cover neurons – a process called remyelination.

Unfortunately, over time, as oligodendrocytes are destroyed and overwhelmed by the power of the autoimmune response, without which there is no production of myelin to cover the neurons, the remyelination stops and the damage becomes irreversible with the loss of axons.

MS typically affects those between the ages 20-40 years old. Symptoms vary from person to person depending on location of plaques. Symptoms related to bouts worsen over weeks and linger for months without treatment.

Aetiology

The aetiology of MS is unknown, and it is not clear why MS develops in some people and not others. A combination of genetic and environmental factors appears to increase the risk of developing MS, more specifically:

- **Sex:** Women are more than two to three times more likely than men are to have relapsing remitting MS.
- **Genetic mutations:** Mutations in genes encoding HLA-DRB1 which is used to identify and bind foreign molecules.
- **Certain infections:** A variety of viruses have been linked to MS.
- **Vitamin D:** Having low levels of vitamin D and low exposure to sunlight is associated with a greater risk of MS.

Clinical presentation

There are 3 common symptoms of MS (Charcot's Neurologic Triad):

1. Dysarthria - A motor speech disorder in which the muscles used to produce speech are damaged, paralyzed, or weakened.

- A result of plaques in the brainstem that effect nerve fibers which control muscles in the mouth and throat.
- Interferes with:
  - Conscious movements (eating and unclear speech even leading to a stutter)
  - Unconscious movements (swallowing)

2. Nystagmus - Involuntary eye movements

- Due to plaques in nerves of the eyes.
- Plaques around the optic nerve, cause blurring or greying of vision, a dark point in the center of vision and even loss of vision in one or both eyes due to damage to optic nerve = optic neuritis.
- Damage to nerves controlling eye movements, causes painful eye movements or double vision if the eyes no longer move in a coordinated manner.

3. Intention Tremor

- Due to plaques along the motor pathways in the spinal cord which can affect outbound signals like skeletal muscle control.
- Motor symptoms include muscle weakness, spams, tremors, and ataxia (loss of balance and coordination). In serious cases this leads to paralysis.

Additional signs and symptoms include:

- Plaques in the sensory pathways which can affect inbound signals, like sensations from the skin which can cause numbness and pins-and-needles.
- Plaques in the autonomic nervous system which can lead to bowel and bladder symptoms (constipation and urinary incontinence) as well as sexual symptoms like sexual dysfunction.
- MS can also affect higher order activities of the brain which can cause poor concentration and critical thinking, as well as depression and anxiety.

There are 4 types of MS based on the pattern of symptoms over time:

1. Relapsing-remitting (RRMS)

- Most common pattern of MS.
- Alternating periods of auto-immune attacks which occur months or years apart and recovery.
- Increase in level of disability due to incomplete remyelination.
- No increase in disability between bouts.

2. Secondary Progressive (SPMS)

- Initially like RRMS, but over time the auto- immune attacks becomes constant.
- This leads to a steady progression of disability.

3. Primary Progressive MS (PPMS)

- Is a constant auto-immune attack on myelin.
- This leads to a steady progression of MS in a person's lifetime.

4. Progressive Relapsing (PRMS)

- A constant auto-immune attack with periods superimposed.
- This leads to disability progressing even faster.

Diagnosis

MS is suspected when there are several neurologic symptoms spread out over:

- SPACE: different locations in the nervous system
- TIME: separate bouts followed by remission

Supported by:

- MRI of the brain and spinal cord which shows multiple CNS lesions called white matter plaques since these regions have a lot of myelin.
- Spinal tap/lumbar puncture which shows the presence of high levels of antibodies in the cerebro-spinal fluid which indicates an autoimmune process.
- Visual Evoked Potential which measures the nervous system's response to visual stimuli.

Treatment

Currently, there is no cure for MS. Treatments such as immuno suppressive therapies, can help speed up recovery folllowing an episode, modify the course of the disease and manage specific symptoms. Physical therapy and cognitive rehabilitation therapy are helpful with sensory, motor, and cognitive functions particularly. Progressive MS is more difficult to treat then RRMS. Immunosuppressive therapy with RRMS is more effective as it lessens the severity and occurrence of relapses.

Trials have been conducted using autologous haematopoietic stem cell transplantation with high-dose immunosuppressive therapy for RRMS. It was found that this was effective in inducing sustained remissions of active RRMS over 5 years.

Another trial showed that it is clinically feasible to use umbilical cord tissue- derived mesenchymal stem cells in the treatment of MS. Intravenous infusions of these stem cells for subjects with MS is safe, and potential therapeutic benefits should be further investigated.

Much research still has to be conducted but preliminary results suggest that both haematopoietic and mesenchymal stem cells have potential as a therapy for MS in the future.

Questions for CPD points

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