

Venous Neurovascular Pathways to Neuroinflammation in Neurodegenerative Disorders

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Alois Alzheimer first notice in 1907 that the disease that bears his name could be caused by micro vascular changes. Neuroinflammation, has been considered as a hallmark of Alzheimer's disease. The presence of anatomic or functional central nervous system's venous stenosis, leads, to actual or functional capillary venous hypertension due to reflected pressure waves. This results in dysfunction of tight junctions, perivenous edema and compromised blood-brain-barrier (BBB) function, affecting parenchymal homeostasis, causing astrocyte and oligodendrocyte dysfunction and perpetuating neurodegeneration. Increased filtration pressure due to venous hypertension and intravascular fluid and protein leakage due to BBB breakdown can lead to increases in interstitial fluid (ISF). Lymphatic drainage of the Central Nervous System (CNS) regulates the balance of ISF and solutes within the CNS microenvironment and represents an accessory route through which excess fluid and proteins can flow from the interstitial spaces back into the blood. Also, plays an important role in neuroimmunological reactions, through physiological drainage of antigens from the brain to regional lymph nodes, mostly cervical and lumbar. In other words, altered lymph flow due to increased production or decreased outflow may affect both neuronal milieu and immune response. The molecular basis of the link between Neurovascular change and Neurodegenerative disorders may determine future therapeutic approaches [1].

In the theoretical framework the presence of anatomic or functional central nervous system's impaired venous drainage leads to actual or functional capillary venous hypertension also due to reflected pressure waves. This results in dysfunction of tight junctions, perivenous edema and compromised BBB function, affecting parenchymal homeostasis and causing astrocyte and oligodendrocyte dysfunction. Increased filtration pressure due to venous hypertension and intravascular fluid and protein leakage due to BBB breakdown can lead to increases in interstitial fluid (ISF). Any factor that increases interstitial fluid also increases lymph flow [2]. Lymphatic drainage of the CNS regulates the balance of ISF and solutes within the CNS microenvironment and represents an accessory route through which excess fluid and proteins can flow from the interstitial spaces back into the blood. It also plays an important role in neuroimmunological reactions through physiological drainage of antigens from the brain to regional lymph nodes, mostly cervical and lumbar [3]. In other words, altered lymph flow due to increased production or decreased outflow may affect both neuronal milieu and immune response.

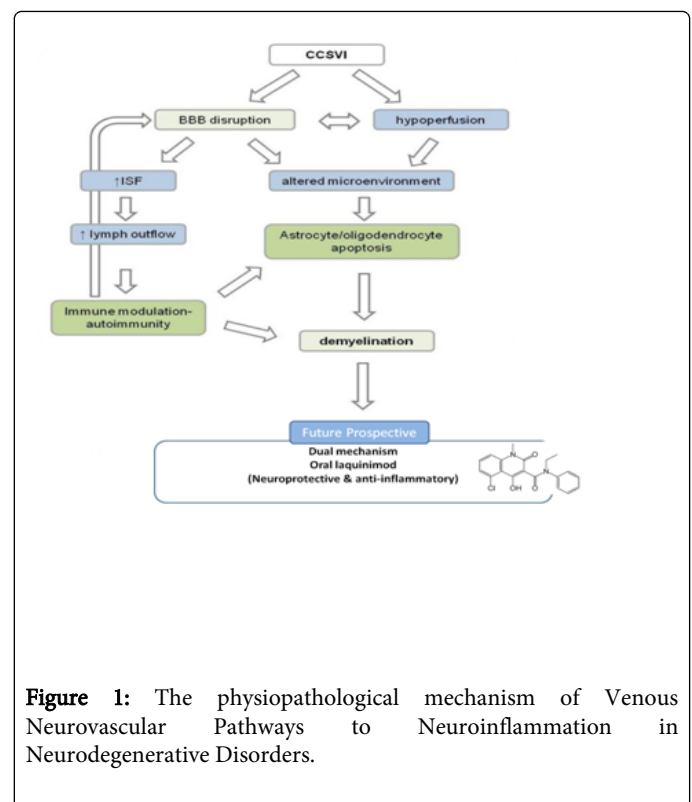


Figure 1: The physiopathological mechanism of Venous Neurovascular Pathways to Neuroinflammation in Neurodegenerative Disorders.

- The physiopathological mechanism has as follow (Figure 1).
- Abnormal neurovascular outflow creates localized increase in intravascular pressure at the venous and of the capillary bed (local hypertension) which provokes rupture of endothelial tight junctions and BBB breakdown [4]. Increased venous capillary pressure lead to Hypo perfusion and virtual Hypoxia [5].
- Increased filtration pressure due to venous hypertension and intravascular fluid and protein leakage due to BBB breakdown can lead to increases in interstitial fluid.
- Any factor that increases interstitial fluid also increases lymph flow [6].
- Fraction of CSF drains through the cribriform plate into the nasal submucosa and ultimately to cervical lymph nodes [7].
- NMO-IgG target the protein aquaporin 4 in the cell membranes of astrocytes which acts as a channel for the transport of water across the cell membrane. Aquaporin 4 is found in the processes of the astrocytes that surround the blood-brain barrier [8].

- BBB break down+Hypoperfusion lead to significant changes in neuronal microenvironment, increased ISF and lymph production, local activation of the inflammatory cascade, iron deposition, oligodendrocyte loss, attraction of phagocytes, demyelination and eventually plaque formation [9].

In conclusion the treatment of venous abnormalities would attenuate this process by alleviating venous hypertension and BBB damage. Thus, a combined haemodynamic-immune paradigm of central nervous system's venous insufficiency emerges, which may explain its potential role in neurodegenerative diseases, such as Alzheimer's disease and provide a theoretical framework for future research. The decreased perfusion pressure would also result in decreased ISF and lymph production and ultimately in decreased antigen transport and presentation to regional lymph nodes. The closing remarks in this short commentary is that a combined haemodynamic-immune paradigm of CNS insufficiency emerges, which may have a role in Neurodegenerative disorders, such as Alzheimer's disease and provide a theoretical framework for future research.

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