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Relationship between Hepatitis C Virus Infection and Peripheral Neuropathy

Ahmed Hamdy Abd El Hameed Mohamed, Hosni Hassan Abdallah Salama, Magdy Omar El Sheikh and Mohamed Salah Mohamed

Neurosurgery Department, Faculty of Medicine- Zagazig University, Egypt

Corresponding Author: Ahmed Hamdy Abd El Hameed Mohamed

E-Mail: ahmedhamdy050@gmail.com

Abstract:

Background: Hepatitis C virus (HCV) infection is a major global health problem, affecting approximately 58 million people worldwide. While its primary target is the liver, HCV is increasingly recognized as a systemic disease with a wide spectrum of extrahepatic manifestations. One of the most clinically relevant complications is peripheral neuropathy, which may arise due to direct viral neurotropism, immune-mediated mechanisms, or metabolic alterations. Peripheral neuropathy in HCV patients often manifests as sensory disturbances, pain, or motor deficits, significantly impacting quality of life and long-term prognosis. Understanding this relationship is essential for early recognition, targeted management, and improved patient outcomes.

Keywords: Hepatitis C virus; Peripheral neuropathy; Extrahepatic manifestations; Cryoglobulinemia; Neurological complications; HCV neuropathy.

Introduction:

Hepatitis C virus (HCV) infection is frequently associated with extrahepatic manifestations, among which peripheral neuropathy (PN) is one of the most common, occurring in a significant proportion of affected individuals **(1).**

The underlying mechanisms remain incompletely understood, but PN in HCV patients—particularly those with mixed cryoglobulinemia—appears to involve immune-complex–mediated vasculitis and ischemia of the vasa nervorum, leading to nerve injury **(1).**

Epidemiologically, PN affects approximately half of chronic HCV patients, with prevalence rates influenced by age, duration of illness, and viral load (Pan-African cohort), underscoring the importance of routine neurological screening in this population **(2).**

Successful eradication of HCV using direct-acting antiviral agents (DAAs) may lead to improvement in neuropathy in some patients, although the extent of recoverability seems limited—particularly in cases with longstanding or severe nerve damage **(3).**

Peripheral neuropathy (PN) is recognized as an extrahepatic manifestation of chronic Hepatitis C virus (HCV) infection. This signifies that PN is a health problem occurring outside the liver which is either directly or indirectly caused by the virus itself or the body's immunological response to it **(4).**

HCV is a bloodborne virus that primarily targets the liver, and if left untreated, it can lead to chronic hepatitis, cirrhosis, and eventually hepatocellular carcinoma. Concurrently, peripheral neuropathy (PN) refers to damage affecting the peripheral nerves—those outside the brain and spinal cord. This damage manifests through symptoms such as numbness, tingling sensations (paresthesias), pain, which is often described as burning or shooting, muscle weakness, and disruptions in autonomic nervous system function. The connection between chronic HCV infection and PN is significant, as HCV is a notable cause of peripheral neuropathy, especially involving types associated with immune system activation. Therefore, recognizing this link is vital for accurate diagnosis and effective management strategies **(5).**

The frequency of PN among individuals suffering from chronic HCV infection varies considerably across different studies, with reported rates ranging from as low as 2% to over 50%. Several factors contribute to this wide variation, including the specific criteria used to define and diagnose PN (whether based solely on symptoms or confirmed with nerve conduction studies), the characteristics of the population being studied (such as the presence of co-existing health conditions), and crucially, the presence or absence of cryoglobulinemia. Notably, patients who have HCV-associated cryoglobulinemia demonstrate a significantly higher prevalence of peripheral neuropathy **(6).**

The nerve damage observed in HCV-associated PN is predominantly considered to be immune-mediated, rather than resulting from direct viral invasion of the nerve tissues, although this point remains a subject of some debate. The primary mechanisms implicated include Mixed Cryoglobulinemia Syndrome (MCS), chronic inflammation/immune dysregulation, and less commonly, direct viral effects **(4).**

A prominent mechanism is Mixed Cryoglobulinemia Syndrome (MCS), which is the most common and well-understood pathway. Cryoglobulins are abnormal immune proteins (immunoglobulins) that have the property of precipitating or forming a gel-like substance in cold temperatures. In the context of HCV, these are typically "mixed" cryoglobulins (Type II or III), comprising polyclonal IgG and either monoclonal or polyclonal IgM possessing rheumatoid factor activity, often found complexed with HCV antigens and viral RNA. The process by which MCS leads to PN involves several steps: HCV stimulates B-cells, resulting in the production of these cryoglobulins and the formation of immune complexes. These complexes then deposit within the walls of small-to-medium sized blood vessels, particularly the vasa nervorum, which supply blood to the nerves. This deposition triggers the complement cascade and attracts inflammatory cells, leading to inflammation and damage of the blood vessel walls, a condition known as cryoglobulinemic vasculitis. The resulting vasculitis causes narrowing or blockage of the vasa nervorum, which reduces blood flow (ischemia) to the peripheral nerves. Ultimately, this lack of adequate oxygen and nutrients damages the nerve fibers, affecting both the axons and potentially the myelin sheath **(5).**

Even in the absence of detectable cryoglobulins, chronic HCV infection fosters a pro-inflammatory state within the body. This chronic inflammation and immune dysregulation represent non-cryoglobulinemic mechanisms contributing to PN. Elevated levels of inflammatory cytokines, such as TNF-alpha and IL-6, may directly or indirectly contribute to nerve damage. Furthermore, autoimmune processes, potentially triggered by the persistent viral infection, might target components of the nerves **(4).**

While HCV RNA has occasionally been detected within nerve tissue or cerebrospinal fluid, the hypothesis that direct viral replication within nerve cells is a primary cause of PN is considered less likely compared to the well-documented immune-mediated mechanisms **(6).**

Other factors can also play a role. Patients with HCV often possess additional risk factors for PN, including diabetes mellitus, alcohol abuse, co-infection with HIV, nutritional deficiencies (like vitamin B12 deficiency), and advanced age. These co-morbidities can either potentiate or complicate the course of HCV-related PN. Historically, interferon-based treatments for HCV were known to sometimes induce or worsen PN, though this is a less frequent concern with the modern Direct-Acting Antivirals (DAAs) **(7).**

Peripheral neuropathy in HCV patients can manifest in several distinct patterns. The most common overall pattern is a distal symmetric sensory or sensorimotor polyneuropathy. While often associated with cryoglobulinemia, it can occur independently. Symptoms typically begin in the feet and gradually progress upwards, following a characteristic "stocking-glove" distribution. Sensory symptoms are predominant and include numbness, tingling (paresthesias), burning pain, and loss of sensation. Motor symptoms, such as weakness, are generally less common than sensory ones, usually mild, affect distal muscles, and the condition often progresses slowly **(4).**

Another significant pattern is mononeuritis multiplex (also known as multiple mononeuropathy), which is highly suggestive of underlying vasculitis, frequently cryoglobulinemic vasculitis. This condition is characterized by damage to individual, non-contiguous peripheral nerves, often presenting acutely or subacutely.

The specific symptoms depend entirely on the nerves affected; examples include foot drop due to peroneal nerve damage or wrist drop from radial nerve damage, alongside sensory loss confined to the distribution of a specific nerve. The presentation is typically asymmetric and tends to progress in a stepwise fashion**(6).**

Small Fiber Neuropathy (SFN) affects the small myelinated (Aδ) and unmyelinated (C) nerve fibers. It primarily causes sensory symptoms like burning pain, aching, prickling, or electric shock sensations, which are often worse at night. SFN may also involve autonomic dysfunction, leading to changes in sweating patterns, skin color alterations, gastrointestinal motility issues, or orthostatic intolerance. Standard nerve conduction studies (NCS) may appear normal in SFN. Diagnosis often relies on specialized tests like quantitative sudomotor axon reflex testing (QSART) or a skin biopsy to assess intraepidermal nerve fiber density **(8).**

Less common patterns of neuropathy associated with HCV include cranial neuropathies, generalized autonomic neuropathy, and radiculopathy **(9).**

Diagnosing HCV-associated PN requires a systematic approach. The process begins with confirming the HCV infection itself through HCV antibody testing and measurement of HCV RNA viral load. A thorough clinical evaluation is essential, involving a detailed history of the patient's symptoms (including onset, distribution, and nature) and a comprehensive neurological examination to assess sensation, strength, and reflexes. It is crucial to exclude other potential causes of peripheral neuropathy. This typically involves blood tests to check for diabetes (HbA1c), vitamin B12 and folate levels, thyroid function, kidney function, autoimmune markers (like ANA and ENA), HIV status, and screening for alcohol abuse **(4).**

Specific testing for cryoglobulins is important, requiring careful blood sample handling (kept warm until serum separation) to ensure accuracy. Measurement of complement levels (C3, C4), which are often low in MCS, and Rheumatoid Factor (frequently positive in MCS) can provide further supportive evidence. Electrophysiological studies, including nerve conduction studies (NCS) and electromyography (EMG), are valuable tools. They help confirm the presence of peripheral neuropathy, characterize its type (distinguishing between axonal loss and demyelination, and identifying sensory versus motor involvement), assess the distribution pattern (differentiating symmetric polyneuropathy from mononeuritis multiplex), and aid in gauging the overall severity. Findings often reveal axonal loss, particularly in sensory nerves, and asymmetric results can suggest mononeuritis multiplex or vasculitis **(6).**

In cases where vasculitis is strongly suspected, especially in the context of mononeuritis multiplex, and other diagnostic tests remain inconclusive, a nerve biopsy may be considered. This typically involves biopsying the sural nerve, a sensory nerve located at the ankle. The biopsy can provide direct evidence of vasculitis (showing inflammation in vessel walls, fibrinoid necrosis), immune complex deposition, and consequent nerve fiber damage (such as axonal degeneration or ischemia). However, it is an invasive procedure with potential side effects like persistent numbness. For diagnosing suspected Small Fiber Neuropathy, a skin biopsy to quantify intraepidermal nerve fiber density is utilized **(8).**

The management strategy for HCV-associated PN focuses on two main goals: treating the underlying cause (the HCV infection) and managing the neuropathic symptoms. Treating the HCV infection is the cornerstone of therapy. Direct-Acting Antivirals (DAAs) are highly effective, achieving cure rates exceeding 95%, and are generally well-tolerated. By eradicating the virus, DAAs remove the primary trigger for immune activation and cryoglobulin production. Studies have demonstrated that successful HCV eradication with DAAs can lead to the improvement or stabilization of PN symptoms and nerve function in many patients, particularly when treatment is initiated early. Often, an improvement in cryoglobulin levels precedes noticeable clinical neurological improvement **(9).**

If cryoglobulinemic vasculitis is present, especially in cases of severe or rapidly progressive vasculitic neuropathy, immunosuppressive therapy may be necessary in addition to the antiviral treatment. Options for managing vasculitis include corticosteroids to quickly reduce inflammation, and Rituximab, a monoclonal antibody targeting B-cells, which is effective in reducing cryoglobulin production and is often used for moderate-to-severe MCS. For very severe, life- or organ-threatening vasculitis, Cyclophosphamide or Plasma Exchange

may be reserved. The timing of initiating immunosuppressive therapy is important; it is often started before or concurrently with DAAs in severe cases **(7).**

Symptomatic management of neuropathic pain is crucial for improving quality of life, although it does not address the underlying nerve damage. Medications commonly used include anticonvulsants (such as Gabapentin and Pregabalin), antidepressants (including Tricyclics like Amitriptyline and SNRIs like Duloxetine and Venlafaxine), topical agents (like Lidocaine patches and Capsaicin cream), and opioids, which should be used cautiously and typically reserved for severe, refractory pain. Non-pharmacological approaches also play a role, encompassing physical therapy and Transcutaneous Electrical Nerve Stimulation (TENS) **(10).**

The prognosis for individuals with HCV-associated peripheral neuropathy is variable. Early diagnosis of the condition and prompt treatment of the underlying HCV infection with DAAs offer the best chance for stabilization or improvement of the neuropathy. However, complete resolution of neuropathic symptoms is less common, particularly if the nerve damage was severe or had been present for a long duration before HCV treatment commenced. Some degree of permanent nerve damage may persist. Neuropathy associated with severe vasculitis, such as mononeuritis multiplex, carries the risk of significant long-term disability if not treated promptly and effectively. Even after successful viral clearance, ongoing symptomatic management often remains crucial if neuropathic pain or functional deficits persist **(11).**

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