



GLOBAL YEAR AGAINST NEUROPATHIC PAIN

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Painful HIV-Associated Sensory Neuropathy

Neuropathic Pain

Neuropathic pain (see the fact sheet on “What Is Neuropathic Pain?”) can result from nerve injury or disease affecting the peripheral or central somatosensory nervous systems.

Definition

- HIV-associated sensory neuropathy (HIV-SN) is a distal symmetrical polyneuropathy that develops in individuals infected with the human immunodeficiency virus (HIV). The neuropathy is commonly painful.
- The terms HIV-associated distal symmetrical polyneuropathy (HIV-DSP) and antiretroviral toxic neuropathy (ATN) are sometimes used when referring to HIV-SN. HIV-DSP typically describes neuropathy that develops before any exposure to neurotoxic antiretroviral drugs. ATN describes neuropathy that coincides with starting antiretroviral therapy, and this drug exposure is presumed to be the inciting event. There are no clear differences in the clinical features of ATN and HIV-DSP.

Clinical Features

- Between 40% and 90% of patients report having pain, which often is “burning” in character.
- Other common symptoms include numbness and paresthesia (e.g., pins-and-needles and tingling).
- Symptoms are typically experienced, in common with other distal symmetrical polyneuropathies, in the feet and sometimes the hands.
- Bedside clinical examination typically reveals the bilateral presence of one or more of the following signs in a “stocking and glove” distribution: altered pinprick sensation, absent or reduced deep-tendon reflexes, and an absent or reduced sense of vibration.

Epidemiology

- HIV-SN is the most common cause of peripheral nerve dysfunction in HIV-infected individuals.
- The neuropathy affects between 30% and 60% of ambulatory HIV-positive individuals, meaning that an estimated 10.5 to 21 million individuals have the neuropathy and are at a high risk of having pain.
- Increasing age and height, any exposure to neurotoxic antiretroviral drugs (e.g., stavudine and didanosine), and worsening infection in individuals not on antiretroviral therapy have been consistently identified as risk factors for developing the neuropathy.
- Despite the strong association between HIV-SN and neurotoxic antiretroviral use, the neuropathy still affects about 45% of individuals only ever exposed to newer therapies.
- Other possible risk factors include exposure to other causes of peripheral neuropathy (e.g., having diabetes mellitus or receiving isoniazid therapy for tuberculosis infection), being female, and using protease inhibitors.
- Important risk factors for developing a painful HIV-SN include having asymptomatic HIV-SN, exposure to neurotoxic antiretroviral drugs, and having major depression.
- Higher viral load, reduced intraepidermal nerve fiber density, and higher levels of pain catastrophizing are associated with greater pain intensity in individuals with painful HIV-SN.

Impact

- Painful HIV-SN is associated with lower health-related quality of life, lower independence in activities of daily living, and increased risk of having major depression.
- Pain severity is positively correlated with poorer quality of life and with greater dependence, unemployment, and depressive symptoms.

Pathogenesis

- The pathogenesis of HIV-SN has yet to be fully explained.
- HIV-DSP is likely to be a result of interactions between HIV, chemokine-like molecules, and host immune cells (particularly macrophages) that release neurotoxic cytokines. The ultimate consequence of this process is a “die-back” axonopathy.



- ATN is likely to result from disruption of mitochondrial function by neurotoxic antiretroviral drugs, which contributes to the development of the neuropathy in susceptible individuals. A diagnosis of ATN does not exclude the possibility of pre- or coexisting nerve fiber damage by the mechanisms thought to be responsible for HIV-DSP.
- Genetic studies support a role for mitochondrial dysfunction and inflammation in the pathogenesis of HIV-SN.

Treatment

- There is evidence of a strong placebo response in clinical trials of analgesics tested in patients with painful HIV-SN compared to other neuropathic pain conditions.
- This strong placebo response has complicated attempts to identify treatments that are superior to placebo at relieving the painful symptoms of the neuropathy. Thus, there is a lack of evidence to support the use of many drugs shown to be beneficial in other neuropathic pain states, such as postherpetic neuralgia and painful diabetic polyneuropathy. Only the high-dose capsaicin patch has some evidence of efficacy superior to placebo.

References

1. Dorfman D, George MC, Schnur J, Simpson DM, Davidson G, Montgomery G. Hypnosis for treatment of HIV neuropathic pain: a preliminary report. *Pain Med* 2013;14:1048–56.
2. Ellis RJ, Rosario D, Clifford DB, McArthur JC, Simpson D, Alexander T, Gelman BB, Vaida F, Collier A, Marra CM, Ances B, Atkinson JH, Dworkin RH, Morgello S, Grant I. Continued high prevalence and adverse clinical impact of human immunodeficiency virus-associated sensory neuropathy in the era of combination antiretroviral therapy: the CHARTER Study. *Arch Neurol* 2010;67:552–8.
3. Kamerman PR, Moss PJ, Weber J, Wallace VCJ, Rice ASC, Huang W. Pathogenesis of HIV-associated sensory neuropathy: evidence from in vivo and in vitro experimental models. *J Peripher Nerv Syst* 2012;17:19–31.
4. Kamerman PR, Wadley AL, Cherry CL. HIV-associated sensory neuropathy: risk factors and genetics. *Curr Pain Headache Rep* 2012;16:226–36.
5. Phillips TJC, Brown M, Ramirez JD, Perkins J, Woldeamanuel YW, Williams ACDC, Orengo C, Bennett DLH, Bodi I, Cox S, Maier C, Krumova EK, Rice ASC. Sensory, psychological, and metabolic dysfunction in HIV-associated peripheral neuropathy: a cross-sectional deep profiling study. *Pain* 2014;155:1846–60.
6. Phillips TJC, Cherry CL, Cox S, Marshall SJ, Rice ASC. Pharmacological treatment of painful HIV-associated sensory neuropathy: a systematic review and meta-analysis of randomised controlled trials. *PLoS One* 2010;5:e14433.