Risk factors for HIV-distal symmetrical polyneuropathy: A review

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Abstract

Objective: To review the risk factors of HIV distal symmetrical polyneuropathy. Methods: A MEDLINE search of the English-language literature using a combination of words (HIV, neuropathy, risk factors) was used to identify original studies, consensus statements, and reviews published in the last 20 years. Results: The various risk factors for HIV-distal symmetrical polyneuropathy. Conclusion: Some of these risk factors are amenable to treatment. Identification of these can go a long way in preventing or delaying the onset of DSPN in these patients thus improving their quality of life.

Keywords: Risk factors, HIV, distal, Polyneuropathy.

INTRODUCTION

Distal symmetrical polyneuropathy (DSPN) is the commonest neurological manifestation of human immunodeficiency virus (HIV) infection [1,2]. With the rising incidence of HIV and its attendant complications, the burden of this complication, the effect on patients’ quality of life is expected to increase.

Identification of a risk factor for a disease condition can go a long way in preventing the disease from occurring if appropriate preventive measures are instituted where possible. Some of these risk factors are host-related others are virus-mediated. Several studies have been carried out to find the risk factors for HIV-DSPN. Some studies have identified consistent risk factors while others have given inconclusive and sometimes conflicting results. We present the various risk factors that are associated with this neurologic complication with significant morbidity and negative impact on the quality of life of those affected.

Risk factors for HIV neuropathy

Age
Sex
Height
Genetics
Antiretroviral drugs
Drugs
Advanced disease
CD4 counts
Plasma RNA levels (viral load)
Serum albumin
Markers of immune activation
Miscellaneous

Age

Age is a risk factor for most neurological diseases probably as a result of the nervous systems limited capacity for regeneration after any insult [3]. Peripheral nerves are metabolically stressed cells that are
very vulnerable to toxicity and damage. Aging appears to increase this vulnerability making it one of the most notable and consistent risk factors for peripheral neuropathy [4]. A study supports other observations about the importance of age to neuropathy risk in HIV. Schifitto et al [5] showed that CD4 nadir is related to neuropathy in a cohort of HIV-infected persons above age fifty years.

Sex

An individual’s sex has not been found to be a risk factor from several studies [6]. However, a phase III trial for the use of nerve growth factor for the treatment of HIV-associated DSPN had 98% of the enrolled participants as men [7]. More research is needed to investigate the effect of sex on the development of DSPN in persons with HIV.

Height

A study showed that increasing height is with an increased risk of developing distal symmetrical polyneuropathy from antiretroviral therapy (antiretroviral toxic neuropathy) [8]. Two-thirds of the patients asymptomatic for neuropathy above 40 years, with height above 1.7 m developed neuropathy following stavudine therapy. Another study that investigated the risk factors for HIV PNP and symptomatic peripheral neuropathy confirmed the clinical impression that neuropathy in HIV is length-dependent with a small, but consistently significant occurrence in taller persons [9].

Genetic factors

Genetic factors may also be important. Corder et al [10] found an increased risk for neuropathy in HIV infected individuals that are heterozygous for apolipoprotein E-4 allele. The postulated mechanisms for the increased risk of peripheral neuropathy include: direct toxic effects of viral proteins (such as gp120) for neurons, increased expression of APOE needed for repair, and ineffective repair in E4 (+). The response of the nervous system to HIV infection may be at least in part genetically determined by the presence or absence of the gene encoding the APOE E4 [11]. Polymorphism of IL-4 has also been associated with sensory neuropathy in Africans with HIV [12, 13].

Advanced disease

DSPN is more frequent in advanced HIV due to increased viral replication and the resultant immune dysregulation [13]. Peripheral nerve pathologies are present in nearly all patients with AIDS. The pathology develops graduallly. Subclinical or silent nerve damage may be present in asymptomatic HIV persons [14]. A low incidence of peripheral neuropathy has been reported in men with early stage HIV infection, and a higher incidence in those with advanced disease [15]. A study had shown that the risk of AIDS-related death associated with a neurologic disorder was increased by 13.3% per 100 cells/mm³ decrement in blood CD4 T-cell levels or by 39% per 10-fold increment in plasma viral load [16].

Antiretroviral use

Deoxyribonucleoside analog use causes a toxic neuropathy clinically indistinguishable from HIV-associated DSPN [17, 18]. In Zambia, 32.2% of the HIV-positive clinic patients self-reported experiencing symptoms of peripheral neuropathy before starting antiretroviral therapy (ART). An additional proportion reported the development of new symptoms after commencing ART [19].

Drugs

Several drugs used in the treatment of HIV-related complications may cause DSPN. A majority of patients with lymphoma or Kaposi’s sarcoma treated with chemotherapeutic regimens, particularly vincristine, develop symptoms and signs of DSPN. Peripheral neuropathy may develop in patients treated with isoniazid (INH) for tuberculosis, particularly when pyridoxine is not administered concurrently.

Thalidomide, which is under investigation in the treatment of HIV-associated aphthous ulcer, may also cause DSPN [20]. Statins, widely used in the developed world and particularly in HIV populations with elevated cholesterol and enhanced cardiovascular risk. They have been found to neuropathy in some populations although subsequent studies have not confirmed these findings [21].

Plasma HIV RNA levels or viral load

Several studies have revealed that higher viral load at baseline before highly active anti-retroviral therapy (HAART) leads to higher risk for developing DSPN [22, 23]. Martin et al [24] reported that HIV virological suppression leads to improvement in quantitative thermal thresholds.

Simpson et al [25] carried out a study to determine if there is an association between plasma HIV-1 RNA levels and severity of HIV-DSPN. Two-hundred and thirty-six subjects had plasma HIV-1 RNA load assayed at baseline. Mean and maximum neuropathic pain was assessed once daily by the Gracely pain scale. Quantitative sensory testing (QST) were also carried out on these patients. QST values correlated with baseline HIV RNA levels. Among the 168 subjects with detectable plasma HIV-1 RNA, they found a significant correlation between plasma HIV-1 RNA and the severity of maximum and global pain, and toe cooling thresholds. Maximum and global pain assessment correlated with plasma HIV-1 RNA in individuals with detectable viral load. Hence, they concluded that there is an association between plasma HIV-1 RNA levels and the severity of pain and QST results in HIV-associated DSP.

CD4+ count

CD4+ T-lymphocyte are coordinators of the body’s immune response. They occupy a central position in regulating immune functions by providing help to B cells in the production of antibody. They also boost as cellular immune response to antigens. These cells are the primary targets of HIV. The relentless destruction of CD4+ T lymphocytes by HIV, either directly or indirectly, results in the loss of HIV-specific immune response. CD4+ T-lymphocyte (CD4) counts are a standard laboratory marker of disease progression in HIV infection and response to treatment [26, 27].

The relationship between low absolute CD4+ lymphocyte count and neurological complications is well established in the era preceding highly active antiretroviral therapy (HAART) [28]. Individuals with CD4 lymphocyte counts less than 200 cells/mm³ are considered highly vulnerable to neurological complications associated with infection. This risk increases with further reductions in CD4+ Count. HIV-infected persons with CD+4 within or above the normal range are subject to similar neurologic diseases as the HIV-negative population [29]. Findings from Hawaii Aging with HIV revealed that low CD+4 count is a predictor of both cognitive and neurological status in HIV-1 infection [30].

Six-hundred and seventy patients were screened for distal symmetric HIV-associated polyneuropathy in a hospital-based study in Germany using nerve conduction studies and clinical neurologic examination during Centers for Disease Control (CDC) stages 1-3 [31]. Their results show stage related rising prevalence of distal symmetrical polyneuropathy, The prevalence of distal symmetrical polyneuropathy thus correlates with the degree of immunodeficiency.

Low CD4 lymphocyte count is now less frequently encountered among individuals with access to HAART because most guidelines recommend treatment for individuals with CD4 lymphocyte counts below 200 cells/µL [32].
Serum albumin
Serum albumin, a marker of nutritional status has also been correlated with increased risk of developing distal sensory neuropathy [33]. Lower levels of serum albumin have been associated with increased risk of disease progression and mortality lower CD4 counts and serum hemoglobin (a marker of immune function and nutritional status) [34-36].

Markers of immune activation
Markers of immune activation including monocyte chemotractant protein (MCP-1), tumor necrosis factor (TNF)-α, and cell surface markers have consistently been associated with neurological complications [37]. Schiffitto et al [38] conducted a prospective study in a cohort of HIV-infected individuals to determine if baseline HIV viral load and specific markers of immune activation (MCP-1, M-CSF, MMP-2, and TNF) would be valuable predictors of the onset of symptomatic DSPN. They found that in subjects asymptomatic for DSPN at baseline (62.5% of the cohort), CSF M-CSF levels was the only virologic and immunologic markers associated with time to development of symptomatic DSPN over a 2-year follow up period.

Miscellaneous risk factors
Prior neuropathy, diabetes, alcohol, malnutrition, lower physical function scores, substance use, and history of AIDS diagnosis have all been reported to associate with increased risk of HIV-DPSN [39-41].

CONCLUSION
Some of these risk factors are amenable to treatment. Identification of these can go a long way in preventing or delaying the onset of DSPN in these patients thus improving their quality of life.

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