The Journal of Medical Research

Review Article

JMR 2017; 3(1): 39-42
January- February
ISSN: 2395-7565

www.medicinearticle.com
Received: 04-11-2016
Accepted: 17-12-2016

Risk factors for HIV-distal symmetrical polyneuropathy: A review

Alagoma Iyagba[1], Arthur Onwuchekwa[2]*

1 *Department of Internal Medicine, University of Port Harcourt Teaching Hospital, Port Harcourt, Rivers State, Nigeria*

2 *Department of Internal Medicine, University of Port Harcourt Teaching Hospital, Port Harcourt, Rivers State, Nigeria*

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.

***Corresponding author:**
Dr. Alagoma Iyagba
Department of Internal Medicine, University of Port Harcourt Teaching Hospital, Port Harcourt, Rivers State, Nigeria

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. Schiffitto *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].

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 gradually. 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/mm^3 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 cholesterols 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 CD+4 lymphocyte counts less than 200 cells/mm^3 are considered highly vulnerable to neurological complications associated with infection. This risk increases with further reductions in CD+4 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 chemoattractant protein (MCP)-1, tumor necrosis factor (TNF)-α, and cell surface markers have consistently been associated with neurological complications [37]. Schifitto *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 out 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.

Financial support and sponsorship: Nil.

Conflicts of interest: There are no conflicts of interest.

REFERENCES

1. Morgello S, Estanislao L, Simpson D, Geraci A, DiRocco A, Gerits P, *et al.* HIV-associated distal sensory polyneuropathy in the era of highly active antiretroviral therapy: the Manhattan HIV Brain Bank. Archives of Neurology 2004; 16(4):546-51.
2. McArthur JC, Brew BJ, Nath A. Neurological complications of HIV. Lancet Neurology 2005; 4(9):543-55.
3. Kamerman PR, Wadley AL, Cherry CL. HIV-associated sensory neuropathy: risk factors and genetics. Current Pain and Headache Reports 2012; 16(3):226-36.
4. Ellis RJ, Rosario D, Clifford DB, McArthur JC, Simpson D, Alexander T, et al. Continued high prevalence and adverse clinical impact of human immunodeficiency virus-associated sensory neuropathy in the era of combination antiretroviral therapy. Archives of Neurology 2010; 67(5):52-58.
5. Watters MR, Poff PW, Shiramizu BT, Holck PS, Fast KM, Shikuma CM, *et al.* Symptomatic distal sensory polyneuropathy in HIV after age 50. Neurology 2004; 62(8):1378-83.
6. Wright E, Brew B, Arayawichanont A, Robertson K, Samintharapanya K, Kongsaengdao S, et al. Neurologic disorders are prevalent in HIV-positive outpatients in the Asia-Pacific region. Neurology 2008; 71(1):50-6.
7. McArthur JC, Yiannoustos C, Simpson DM, Adornato B, Singer EJ, Hollander H, *et al.* A phase II trial of nerve growth factor for sensory neuropathy associated with HIV infection. Neurology 2000; 54(5):1080-88.
8. Affandi JS, Price P, Imran D, Yunihastuti E, Djauzi S, Cherry CL. Can we predict neuropathy risk before stavudine prescription in a resource-limited setting? AIDS Research and Human Retroviruses 2008; 24(10):1281-4.
9. Evans SR, Ellis RJ, Chen H, Yeh T, Lee AJ, Schifitto G, *et al*. Peripheral neuropathy in HIV: prevalence and risk factors. AIDS 2011; 25(7):919-928
10. Corder EH, Robertson K, Lannfelt L, Bogdanovic N, Eggertsen G, Wilkins J, et al. HIV-infected subjects with the E4 allele for APOE have excess dementia and peripheral neuropathy. Nature Medicine 1998; 4(10):1182-4.
11. Nathan BO, Bellosta S, Sanan DA, Weisgraber KH, Mahley RW, Pitas E. Differential effects of apolipoproteins E3 and E4 on neuronal growth in vitro. Science 1994; 264(5)850-52.
12. Wadley AL, Kamerman PR, Chew CSN, Lombard Z, Cherry CL, Price P. A polymorphysim in IL4 associates with sensory neuropathy in African HIV patients. Molecular Immunology 2013; 55(3):197-199.
13. Luciano CA, Pardo CA, McArthur JC. Recent developments in the HIV neuropathies. Current Opinion in Neurology 2003; 16(3):403-9.
14. Tagliati M, Grinnell J, Godbold J, Simpson DM. Peripheral nerve function in HIV infection: clinical, electrophysiologic, and laboratory findings. Archives of Neurology 1999; 56(1):84-9.
15. Barohn RJ, Gronseth GS, LeForce BR, McVey AL, McGuire SA, Butzin CA, *et al.* Peripheral nervous system involvement in a large cohort of human immunodeficiency virus-infected individuals. Archives of Neurology 1993; 50(2):167-71.
16. Vivithanaporn P, Heo G, Gamble J, Krentz B, Hoke A, Gill MJ, Power C. Neurologic disease burden in treated HIV/AIDS predicts survival .A population-based study. Neurology 2010; 28(75):1150-8
17. Dalakas MC. Peripheral neuropathy and antiretroviral drugs. Journal of the Peripheral Nervous System 2001; 6(1):14-20.
18. Moyle GJ, Sadler M. Peripheral neuropathy with nucleoside antiretrovirals. Drug Safety 1998; 19(6):481-94.
19. Birbeck GL, Chomba E, Kvalsund M, Bradbury R, Mang'ombe C, Malama K and the RAAZ Study Team. Antiretroviral adherence in rural Zambia: the first year of treatment availability. The American Journal of Tropical Medicine and Hygiene 2009; 80(4):669-74.
20. Ochonisky S, Verroust J, Bastuji-Garin S, Gherardi R, Revuz J. Thalidomide neuropathy incidence and clinico-electrophysiologic findings in 42 patients. Archives of Dermatology 1994; 130(1):66-69.
21. Gaist D, Jeppesen U, Andersen M, Garcia Rodriguez LA, Hallas J, Sindrup SH. Statins and risk of polyneuropathy: a case-control study. Neurology 2002; 58(9):1333-37.
22. Lopez OL, Becker JT, Dew MA, Caldararo R. Risk modifiers for peripheral sensory neuropathy in HIV infection/AIDS. European Journal of Neurology 2004; 11(2):97-102.
23. Schifitto G, McDermott MP, McArthur JC, Marder K, Sacktor N, Epstein L, *et al.* Incidence of and risk factors for HIV-associated distal sensory polyneuropathy. Neurology 2002; 58(12):1764-8.
24. Tyor WR, Wesselingh SL, Griffin JW, McArthur JC, Griffin DE. Unifying hypothesis for the pathogenesis of HIV-associated dementia complex, vacuolar myelopathy, and sensory neuropathy. Journal of Acquired Immune Deficiency Syndromes 1995; 9(4):379-88.
25. Simpson DM, Haidicha A, Schittob G, Yiannoutsosa CT, Geraci AP, McArthur JC, Katzenstein DA, ACTG 291 Study Team. Severity of HIV-associated neuropathy is associated with plasma HIV-1 RNA levels. AIDS 2002; 16(3):407-12.
26. Post FA, Wood R, Maartens G. CD4 and total lymphocyte counts as predictors of HIV disease progression QJM 1996; 89(7):505-508.
27. Hunt PW, Brenchley J, Sinclair E, McCune JM, Roland M, Shafer KP, et al. Relationship between T cell activation and CD4+ T cell count in HIV-seropositive individuals with undetectable plasma HIV RNA levels in the absence of therapy. Journal of Infectious Diseases 2008; 197(1):126-33.
28. Childs EA, Lyles RH, Selnes OA, Chen B, Miller EN, Cohen BA, et al. Plasma viral load and CD4 lymphocytes predict HIV-associated dementia and sensory neuropathy. Neurology 1999; 52(3):607-607.
29. Lyons J, Venna N, Cho TA. Atypical nervous system manifestations of HIV. In Seminars in Neurology 2011 Jul (Vol. 31, No. 03, pp. 254-65)
30. Valcour V, Yee P, Williams AE, Shiramizu B, Watters M, Selnes O, *et al*. Lowest ever CD4 lymphocyte count (CD4 nadir) as a predictor of current cognitive and neurological status in human immunodeficiency virus type 1 infection-The Hawaii Aging with HIV Cohort. Journal of Neurovirology 2006; 12(5):387-91.
31. Husstedt IW, Evers S, Reichelt D, Grotemeyer KH, Kammer-Suhr B, Böckenholt S, et al. Screening for HIV-associated distal-symmetric polyneuropathy inCDC-classification stages 1, 2 and 3. Acta Neurologica Scandinavica 2000; 101(3):183-7.
32. Günthard HF, Aberg JA, Eron JJ, Hoy JF, Telenti A, Benson CA, Burger DM, Cahn P, Gallant JE, Glesby MJ, Reiss P. Antiretroviral treatment of adult HIV infection: 2014 recommendations of the International Antiviral Society–USA Panel. JAMA 2014; 312(4):410-25.
33. Feldman JG, Burns DN, Gange SJ, Bacchetti P, Cohen M, Anastos K, *et al*. Serum albumin as a predictor of survival in HIV-infected women in the Women's Interagency HIV study. AIDS 2000; 14(7):863-70.
34. Goldwasser P, Feldman J. Association of serum albumin and mortality risk. Journal of Clinical Epidemiology 1997; 50(6):693-703.
35. Guenter P, Muurahainen N, Simons G, Kosok A, Cohan GR, Rudenstein R,

et al. Relationships among nutritional status, disease progression, and survival in HIV infection. Journal of Acquired Immune Deficiency Syndromes 1993; 6(10):1130-8.
36. Süttmann U, Ockenga J, Selberg O, Hoogestraat L, Deicher H, Müller MJ. Incidence and prognostic value of malnutrition and wasting in human immunodeficiency virus-infected outpatients. Journal of Acquired Immune Deficiency Syndromes 1995; 8(3):239-46.
37. Kusdra L, McGuire D, Pulliam L. Changes in monocyte/macrophage neurotoxicity in the era of HAART: implications for HIV-associated dementia. AIDS 2002; 16(1):31-8.
38. Schifitto G, McDermott MP, McArthur JC, Marder K, Sacktor N, McClernon DR, NEAD Consortium. Markers of immune activation and viral load in HIV-associated sensory neuropathy. Neurology 2005; 64(5):842-48.
39. Cherry CL, Skolasky RL, Lal L, Creighton J, Hauer P, Raman SP, *et al.* Antiretroviral use and other risks for HIV-associated neuropathies in an international cohort. Neurology 2006; 66(6):867-73.
40. Robinson-Papp J, Geiman BB, Grant I, Singer E, Gensier G, Morgello S. Substance abuse increases the risk of neuropathy in an HIV infected cohort. Muscle and Nerve 2012; 45(4):471-76.
41. Lichtenstein KA, Armon C, Baron A, Moorman AC, Wood KC, Holmberg SD, HIV Outpatient Study Investigators. Modification of the incidence of drug-associated symmetrical peripheral neuropathy by host and disease factors in the HIV outpatient study cohort. Clinical Infectious Diseases 2005; 40(1):148-57.