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Correlation between Serum CD4 Count and Neuropathic Pain in HIV / AIDS Patients

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Abstract: ***Peripheral neuropathic pain is a neurological complication frequently met in Human Immunodeficiency Virus (HIV)/Acquired Immune Deficiency Syndrome (AIDS) patients. This study aimed to determine whether the level of serum CD4 and other factors were correlated with neuropathic pain in HIV/AIDS patients. The study was designed as cross-sectional with consecutive sampling in all patients undergoing treatment in Sanglah AIDS research Centre (SARC) during period of March – August 2013. The neuropathic pain was assessed using The Leed Assessment of Neuropathic Symptoms and Sign pain scale (LANSS). From the 46 subjects with HIV, 65.2% was male (n = 30), 34.8% was female (n = 16), with mean age 35.72 years old. The result showed correlation between CD4 count (r = -0.348; p = 0.018), stadium of HIV (r = 0.358; p = 0.014) and duration of ARV treatment (r = 0.330; p = 0.025) and LANSS score. Factors proven to be correlated with neuropathic pain in HIV/AIDS patients are CD4 count, stages of HIV and duration of ARV treatment.***

Keywords: neuropathic pain, correlation, HIV, AIDS, CD4, ARV

1. Introduction

Peripheral neuropathy is the most frequent neurological complication met in Human Immunodeficiency Virus (HIV)/Acquired Immune Deficiency Syndrome (AIDS) patients. Neuropathy can be caused by a primary condition (age, sex), secondary condition (opportunistic infection), and the antiretroviral (ARV) medication used.[1] The most frequent form of in the HIV patients is distal sensory polyneuropathy (DSP), mounted about 35% of all cases of neuropathic complication. The primary etiology of DSP is the virus itself through its effect on the immune system and the antiretroviral drugs used in the treatment of HIV/AIDS and also the length of use, a condition termed Antiretroviral Toxic Neuropathy (ATN).[2,3,4]

HIV neuropathy is a disorder mostly characterized by sensory problem. It manifests either as spontaneous or provoked pain with both sub-acute and chronic etiologies, which often evolves during the late stage period of AIDS. DSP becomes increasingly found in the late immunosuppressive stage during which the virus replication amplifies, added with the combination of dideoxynucleotides uses. DSP is an axonal sensory neuropathy which affects the small fiber nerves.[5,6] The clinical finding includes bilateral pain with a chronic and progressive onset, often described as “numbness”, “tingling”, and “burning” in the lower extremities with a symmetrical pattern, frequently worsens at night or after a walk without significant muscle weakness. Patients also often experience hyperalgesia and allodinia. [7,8]

Prior to Highly Active Anti-Retroviral Therapy (HAART) use, neuropathy was commonly associated with low Cluster of differentiation 4 (CD4) count, high plasma viral load, the stage of HIV and opportunistic infections. [1,7,8] As the science progressed, and with the development of better HAART, more peripheral neuropathies found in the clinical setting. One study cited that the combination of HAART may be the cause of peripheral neuropathy.[9] The pathophysiology of HIV neuropathy, however, is still largely in question. The toxicity of HIV virus’ protein, immune response toward the virus, and the damage to mitochondria as a result of antiretroviral drugs, specifically the nucleoside reverse trancriptase inhibitor (NRTIs), all those are potential for inducing neurotoxicity. These factors, whether alone or in combination, are the principal catalysts for HIV-associated sensory neuropathy (HIV-SN).[8,10] This study aimed to determine whether the serum CD4 count, and other factors, were correlated with neuropathic pain in HIV/AIDS patients.

2. Materials and Methods

This study used cross-sectional design with consecutive sampling method in the HIV/AIDS patients undergoing treatment in Sanglah AIDS research Centre (SARC). The sampling was done until the minimum requirement size based on the minimal sample size formula was met. The study was conducted between March and August 2013. The inclusion criteria were: 1) HIV-positive patient. 2) cooperative and willing to participate in the study by signing the consent form. The exclusion criteria were: 1) Patient with altered level of consciousness, 2) patient with history of stroke, head injury, intracranial tumor, Parkinson, heart disease, hereditary sensorimotor neuropathy, masking neuropathy, 3) risk factors for neuropathic pain such as diabetes mellitus, hypercholesterolemia, hypertension, smoking, alcohol consumption, and uremia.

The variables to be analyzed were the serum CD4 count, the stage of HIV, the type of ARV, and duration of ARV use. To assess the neuropathic pain, the LANSS (The Leed Assessment of Neuropathic Symptoms and Sign pain scale) score, which helps to differentiate nociceptive pain from neuropathic pain based on the sensory picture and bedside examination, and is also practical to give rapid information. (Martinez-Lavin et al., 2003). The Indonesian version of LANSS score has proven to be valid and reliable.[11] LANSS comprises of 5 descriptive sensory items and 2 sensory dysfunction items. A LANSS score ≥ 12 is classified

as neuropathic pain, while score <12 classified as nociceptive pain.[12] All HIV-positive subjects that met the inclusion and exclusion criteria and who had signed the consent form, were interviewed using structured questionnaire. Datas were analyzed in descriptive manner. Statistical analysis was done using spearman correlation with level of significance p<0,05. Statistical analysis were carried out with SPSS Ver. 16 for windows. Ethical clearance was issued by the Ethical Committee of Udayana University – Sanglah General Hospital.

3. Result

Forty six subjects with HIV/AIDS signed the informed consent. Period of March – August 2013. The neuropathic pain was assessed using The Leed Assessment of Neuropathic Symptoms and Sign pain scale (LANSS). From the 46 subjects with HIV, 30 subjects were male (65,2%) and 16 subjects were female (34,8%), median age was 35,72±9,189. Stadium 4 was the majority of stadium found in the study (76,1%). The most used ARV in the study was combination of azt/3tc/nvp (52,2%). More than 50% of the samples had been on ARV for >1 year. The basic characteristic of the subjects are presented in Table 1.

Table 1: Basic characteristic of the study subjects

Variable	*Number of subject (n)*	*Percentage (%)*
Sex:		
- Male	30	65,2
- Female	16	34,8
Age, mean±SD	35,72 ±9,189	
Weight, mean±SD	57 ±12,681	
Height, mean±SD	163,04 ±9,050	
Stadium of HIV		
- stadium 1	4	8,7
- stadium 2	7	15,2
- stadium 3	0	0
- stadium 4	35	76,1
Type of ARV		
- without ARV	7	15,2
- azt/3tc/nvp	24	52,2
- d4t/3tc/efv	7	15,2
- azt/3tc/efv	5	10,9
- tdf/3tc/nvp	3	6,5
Duration of treatment		
- without ARV	7	15,2
- ≤ 1 year	13	28,3
- > 1 year	26	56,6
CD4 count (Mean, SD)	46 (71,63 ±82,640)	

azt: zidovudin, d4t : Stavudin , 3tc : Lamivudine,
efv: Efavirenz , nvp: Nevirapine, tdf: tenofovir

The correlation test between those factors with the neuropathic pain is presented in table 2. There was weak correlation, albeit significant, between the stadium of HIV (p= 0,014 r=0,358) and duration of treatment (p=0,025 r=0,330), while the serum CD4 count (p=0,018 r=-0,348) had significant weak negative correlation. Weight, height, and type of ARV did not have any significant correlation (p>0,05).

Table 2: Correlation between multiple factors and neuropathic pain

Variable	Coefficient (r)	P value
Serum CD4 count	-0.348	0.018*
Stadium of HIV	0.358	0.014*
Type of ARV	0.077	0.610
Duration of treatment	0.330	0.025*

*statistically significant

4. Discussion

This study showed that CD4 count had a significant weak negative correlation with the neuropathic pain based on the LANSS score (r=-0,348), which means the lesser the CD4 count, the higher the risk of the neuropathic pain is. The CD4 count will decline as the AIDS progresses, marking the severity of the disease and the deterioration of the immune system. Since the early stage of the HIV infection, the CD 4 T lymphocyte cells have been the main target. The direct cytopathic effect of HIV will destroy the CD4 cells and as the CD4 count falls, so does the immunity of the host. The increasing viral load will lead to more severe inflammation and immune response which will ultimately lead to the damage of the central and peripheral nervous system. The lower the CD4 count is, the higher the risk for symptomatic DSP to develop. [13] Schifitto et al. (2002) and Simpson et al. (2006) also showed the same result in their study.[14,15]

In this study, the type of ARV was found to be uncorrelated with neuropathic pain based on LANSS score. This was caused by the advance use of ARV which was known to have lower neuropathic complication. In the prior studies, neuropathic pain was said to be the most frequent complication in ARV use, approximately 30% in both adult and children. The type of ARV that commonly causes neuropathy is the NRTIs, either as a single agent or combination. Didanosine (ddI), zalcitabine (ddC), stavudine (d4T) and zidovudin (AZT) are classified as NRTI.[16]

The stadium of HIV in this study was found to have significant correlation with the neuropathic pain based on the LANSS score, however the correlation was weak(r=0,358). This was similar to the prior studies which stated that the risk for neuropathic pain is higher as the disease progresses. This can be explained by the increase of virus activity in the late stages of HIV, specifically in stadium 3 and 4 where opportunistic infections take place, marking the high viral load and the low CD4 count. In a multi-center cohort study, the risk for DSP increased two-fold in patients with viral load >10.000 copies/ml.[5,9]

The duration of treatment also had significant correlation with the neuropathic pain, and again the correlation was found to be weak (r=0,330). Previous studies mentioned the longer the duration of ARV use, the higher the risk for the neuropathy. The pathogenesis responsible for this is the mitochondrial toxicity induced by the ARV. NRTIs work by inhibiting the polymerase mitochondrial DNA (mDNA) to prevent the replication of the mDNA responsible for the development of cell. This will cause cell death. The mitochondrial toxicity depends on the dose of the NRTIS and needs considerable time for it to cause the side effect. The

metabolism change of the mitochondria develops slowly over long time, so the chance of this side effect to occur within the first month of NRTIs use is minimal. This damage can also occur in a lengthy use of small dose NRTIs. [1,10]

5. Conclusion

Factors found to have significant correlation with the neuropathic pain were the low CD4 count, the stadium of HIV, and the duration of treatment. Further studies regarding these factors and their correlation with the neuropathic pain in HIV/AIDS patients need to be done with a case-control or cohort design and with bigger population.

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References

[1] Keswani, S.C., Jack, C., Zhou, C., Hoke, A., 2006. Establishment of a Rodent Model of HIV –Associated Sensory Neuropathy, The Journal of Neuroscience, 26(40): 10299-10304
[2] Janis J. Kompliksasi Neurologik HIV, Aspek Petofisiologi, Diagnostik dan Terapi. Neurona 2004;21 : 17-23.
[3] Ferrari,S., Vento, S., Monaco, S., Cavallaro, T., Cainelli, F., Rizutto, N., Temesgen, Z., 2006. Human Imunodefficiency Virus-Associated Periferal Neuropathies, Mayo Clinic Proceeding, 81(2): 213-291.
[4] Verma, S., Estanislao, L., Mintz, L., Simpson, D., 2004. Controlling Neuropathic Pain in HIV, Current HIV/AIDS Reports, 1:136-141.
[5] Pardo, C.A., McArthur, J.C., Griffin, J.W., 2001. HIV Neuropathy: Insight in The pathology of HIV peripheral nerve disease, Journal of the Peripheral Nervous System, 6: 21-27.
[6] Luciano, C.A., Pardo, C.A., McArthur, J.C., 2003. Recent development in the HIV neuropathies, Lippincott & Wilkins, Current Opinion in Neurology, 16:403-409.
[7] Abrams, D.I., Jay, C.A., Shade, S.B., Vizoso, H., Reda, H., Press, S., Kelly, M.E., Rowbotham, M.C., Petersen, K.L., 2007. Cannabis in painful HIV-associated sensory neuropathy, A randomized placebo-controlled trial, Neurology, 68: 515-521.
[8] Gonzalez-Duarte, A., Robinson-Papp, J., Simpson, D.M. 2008. Diagnosis and Management of HIV-associated Neuropathy. Neurol. Clin; 26: 821–832.
[9] Smyth, K., Affandi, J.S., Bowtell-Harris, C., Mijch, A.M., Watson, K., Woolley, I.J., Price, P., Wesselingh, S.L., Cherry, C.L., 2007. Prevalence of and risk factors for HIV-associated neuropathy in Melbourne, Australia 1993-2006, HIV Medicine, 8:367-373.
[10] Kamerman, P.R., Moss, P.J., Weber, J., Wallace, V.C.J., Rice, A.S.C., and Wenlong Huang, W., 2012. Pathogenesis of HIV-associated sensory neuropathy: evidence from in vivo and in vitro experimental models, Journal of the Peripheral Nervous System 17:19–31.
[11] Widyadharma, E., Yudiyanta., 2008. Uji Reliabilitas Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Scale pada Penderita Diabetes Melitus tipe II. CPD Neurodiabetes. Yogyakarta
[12] Bennett, M., 2001. The LANSS Pain Scale: The Leeds assessment of neuropathic pain symptoms and sign, Pain, 92: 147-157.
[13] Devadas, K., Lal, R.B., Dhawan, S., 2005. Immunology of HIV-1. In: Gendelman, H.E., Grant, I., Everall, I.P., Lipton, S., Swindels, S. (eds). The Neurology of AIDS, 2nd ed, Oxford University Press, New York. Pp 29-47.
[14] Schifitto, G., McDermott, M.P., McArthur, J.C., Marder, K., Sacktor, N., Epstein, L., Kieburtz, K., 2002. Incidence of and risk factors for HIV-associated distal sensory polyneuropathy, Neurology, 58: 1764-1768.
[15] Simpson, D.M., Kitch, D., Evans, S.R., McArthur, J.C., Asmuth, D.M., Cohen, B., et al., and the ACTG A5117 Study Group, 2006. HIV neuropathy natural history cohort study: Assessment measures and risk factors, Neurology, 66:1679-1687.
[16] Moore, R.D., Wong, W.E., Keruly, J.C., McArthur, J.C., 2000. Incidence of neuropathy in HIV-infected patients on monotherapy versus those on combination therapy with didanosine, stavudin and hydroxyurea, AIDS, 14:273-278