International Journal of Health Sciences and Research
www.ijhsr.org ISSN: 2249-9571

Review Article

Diagnostic Modalities for HIV Distal Symmetrical Peripheral Neuropathy: A Review

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Received: 03/11/2016 *Revised: 23/11/2016* *Accepted: 25/11/2016*

ABSTRACT

Objective: To review the current diagnostic modalities for HIV-distal symmetrical polyneuropathy (HIV-DSPN), the commonest neurological complication of HIV.
Materials and Methods: A MEDLINE search of the English-language literature using a combination of words (HIV, distal symmetrical, polyneuropathy, diagnosis) to identify original studies, consensus statements, and reviews published in the past three decades. Emphasis was on diagnosis of HIV distal symmetrical polyneuropathy, the most common form
Results: The various modalities available for the diagnosis of HIV-DSPN.
Conclusion: Early screening and diagnosis of distal symmetrical polyneuropathy would facilitate institution of new treatments or modification of antiretroviral therapies. This would in the long-term decrease disease-related morbidity by improving the patient's quality of life.

Keywords: HIV, distal symmetrical, polyneuropathy, diagnosis

INTRODUCTION

Distal symmetrical polyneuropathy is the commonest neurologic complication of human immunodeficiency virus infection. [1] It is a progressive and debilitating disorder characterized by bilateral symmetrical numbness, hypersensitivity, and pain in the feet and lower legs. [2] It causes significant morbidity for patients affecting the quality of life and sometimes causing distressing neuropathic pain. [3,4]

It is usually under-reported by patients and under diagnosed in resource-poor settings. There is no gold standard test for the diagnosis of HIV-DSPN. Several diagnostic modalities can be used depending on the setting and availability of such diagnostic facilities. We describe the various modalities for diagnosing this condition in clinical practice and research settings.

Table: Diagnostic modalities for HIV DSPN

Nerve conduction studies
Nerve biopsy studies
Skin biopsy studies
Quantitative sensory testing
Symptom scores
Autonomic function tests

Nerve Conduction Studies (NCS)

Nerve conduction studies measure the ability of peripheral nerves to conduct electrical impulses and are useful for evaluating diseases of peripheral nerves. [5]They assess large myelinated fiber functions of fine touch, vibration, and proprioception. Hence, small fiber neuropathies that present with pain and temperature impairment may have normal sensory studies. [6] The procedure consists of electrical stimulation of a nerve and recording of the evoked potentials either

from the muscle or the nerve itself. [7]

These tests are however not readily available especially in resource poor setting, require considerable expertise and technical knowledge for performance and interpretation, and require standardization with reference values. [8] Besides several variables can affect a sensory nerve conduction study: patient's age, temperature, limb oedema, sub-maximal or excess stimulation and cathode-anode reversal.

During the early asymptomatic stages of HIV infection, peripheral neuropathies are uncommon, but electrodiagnostic testing shows subclinical evidence of peripheral nerve involvement in about 10 % of cases. [9] The most common abnormality is a reduction in compound amplitude reflecting fewer functioning axons. With myelin relatively intact, the remaining axons normally conduct with normal latencies and conduction velocities. However, as axonal degeneration progresses, latencies can be mildly prolonged, and conduction velocities slightly slowed because of loss of larger, fast conducting fibers. [10]

A study carried out on sixteen HIV-infected patients showed nerve conduction abnormalities in almost all the patients including those who were asymptomatic for neuropathy. [11] Another study involving twenty-eight neurologically asymptomatic men showed nerve conduction abnormalities consistent with a subclinical neuropathy. [12] Hence, subclinical neuropathy is very prevalent in asymptomatic HIV patients.

Skin Biopsy Studies

Skin biopsies with nerve fiber density evaluation have also been shown to be of value in the assessment of peripheral neuropathies with predominant small fiber involvement such as HIV. Reduction in density, increased frequency of varicosities and fragmentation of nerve fibers are prominent features of a skin biopsy from patients with HIV-SN. [13]

Skin biopsy is a safe, almost painless, and cheap technique for evaluating small nerve fibers separately. It has good sensitivity and specificity for diagnosing small fiber. [14] It detects morphological and quantitative changes in skin innervation earlier than nerve conduction tests. It is also very useful for predicting the progression of neuropathy. [15-17] This procedure has also been found useful in making a diagnosis of antiretroviral toxic neuropathy. Patients on treatment with zalcitabine and didanosine have shown a reduction in the density of intraepidermal nerve fibers with an inverse correlation with neuropathic pain intensity. [18]

Nerve Biopsy Studies

Sural nerve biopsy commonly used for the histopathological diagnosis of most inflammatory peripheral neuropathies such as leprosy, vasculitis, and sarcoidosis. It is an invasive procedure performed in the operating room. Its disadvantages are pain and permanent sensory loss distal to the biopsy site. There are however no studies supporting its role for the diagnosis of HIV-DSPN. [19] Its importance may lie in the fact that some of the above named diseases may occur simultaneously with HIV infection.

Quantitative Sensory Tests (Qst)

These make use of calibrated tools to assess the various sensory modalities. Small-fiber function is assessed by perception to cold, temperature and current. Large-fiber function is assessed by perception to vibration, pressure, and joint position. [20] These tests are qualitative measures of sensation. They have been demonstrated to provide a valuable quantitative sensory function in subjects with polyneuropathy. They are limited by the subjected responses provided by the patient during the test procedure.

Vibration perception threshold (VPT) assessment is the commonest QST measure in clinical practice. It is done using a hand-held device called a biothesiometer. The tractor of the device is applied to the tip of the big toe and vibration perception is measured in volts. The vibration perception is abnormal when the mean voltage of three readings exceeds 25 millivolts. [21]

Autonomic Function Tests

Sudomotor function tests include the quantitative sudomotor axon reflex test (QSART), the sweat imprint test, the thermoregulatory test, and the sympathetic skin response. Such tests are very expensive and require expensive equipment and trained personnel. [22]

Symptom Scores

These are questionnaire based modalities for diagnosing distal symmetrical polyneuropathy. They are simple to use, require minimal training and practicable. Before their application in clinical practice, however, they must have been validated against an external standard.

The Brief Peripheral Neuropathy Screen was developed by the AIDS Clinical Trial Group (ACTG). It has been validated in HIV-infected persons using quantitative sensory testing (VPT) and intra-epidermal nerve fiber density as gold standard. [23] It is simple and rapid to administer and focuses on symptoms and signs that are common in this context. It has been widely used in clinical trials, can be administered by non-neurologists following the minimal training, and encompasses both clinical signs and symptoms suggestive of neuropathy. This tool has also been shown in a large cohort of individuals with HIV infection to detect accurately those who have the greatest degree of abnormality on formal sensory threshold testing. These data confirm that patients who test positive for HIV-SN using the BPNS have significantly more dysfunction and pathology of the peripheral nervous system than others with HIV infection, and reinforce the relevance of assessing signs as well as neuropathic symptoms. It can also be used readily by a non-neurologist. [24] The BPNS was designed for use in the context of HIV infection.

This validated neuropathy screening tool was integrated into routine ART visits at an HIV clinic in Mombasa, Kenya. [25] Diagnosis of PN required at least one symptom and either abnormal vibratory sensation or deep tendon reflex bilaterally. Among 102 consecutively screened patients, 63% were women, 62% were receiving ART for < or = 1 year, and 86% were receiving a stavudine (4dT) based regimen. Thirty-seven (37%) of these patients had peripheral neuropathy.

The Single question neuropathy screen (SQNS) is most applicable when an even briefer neuropathy screen is required. Questioning patients about the presence of numbness in the lower extremity has been shown in multiple cohorts to be the single question that is most sensitive and specific for neuropathy.

It was included in the enrollment data for people commencing antiretroviral therapy in publically funded clinics in Zambia. [26] The authors assessed the sensitivity, specificity, positive and negative predictive value of this SQNS against the Brief Peripheral Neuropathy Screen (BPSN) in detecting HIV-associated sensory neuropathy in patients recruited from a rural and an urban hospital in Zambia. The SQNS was asked followed by conduct of the BPNS by the neurology resident assisted by a Zambian healthcare worker and translator. Seventy seven patients [48 (62.3%) urban and 29 (37.7%) rural] were enrolled. The mean age was 33.7 years (range 15-53 years; SD67.81). The SQNS was 95.7% sensitive and 80.0% specific, with 88.2% positive predictive value and 92.3% negative predictive.

Despite its reliance on symptoms alone, this study suggested that the SQNS may be a valid research tool for identifying HIV-associated neuropathy among advanced stage HIV patients in Zambia. The SQNS has not been validated, but its routine availability in existing ARV clinic records in many sub-Saharan clinics makes it a potentially valuable source of epidemiological data on PN among people accessing HIV care value.

The subjective peripheral neuropathy screen (SPNS) is a brief self-report tool that was designed as a screening instrument for sensory neuropathy in HIV-infected subjects by the AIDS Clinical Trial

Group (ACTG). [27]

Significant correlations were demonstrated for SPNS results and a neurologic examination, vibratory quantitative sensory testing, and severity measures. Sensitivity and specificity analysis indicates that numbness of the lower extremities is the symptom reported by the SPNS that most correctly classifies painful sensory neuropathy. [28]

CONCLUSION

Early screening and diagnosis of distal symmetrical polyneuropathy would facilitate institution of new treatments or modification of antiretroviral therapies. This would in the long-term decrease disease-related morbidity by improving the patient's quality of life.

Source of Support: None
Conflict of Interest: None Declared

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How to cite this article: Iyagba A, Onwuchekwa A. Diagnostic modalities for HIV distal symmetrical peripheral neuropathy: a review. Int J Health Sci Res. 2016; 6(12):297-301.

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