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Factors associated with distal symmetric polyneuropathies in adult Zambians: A cross-sectional, observational study of the role of HIV, non-antiretroviral medication exposures, and nutrition

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ABSTRACT

Background: Non-antiretroviral (ART) drug exposures and poor nutrition may be important modifiable risk factors for distal symmetric polyneuropathies (DSP) in sub-Saharan Africa.
Methods: We conducted a cross-sectional study of DSP prevalence and factors associated with DSP among clinic attendees in urban and rural Zambia. All participants underwent neurologist-performed examination. Laboratory investigations seeking comorbid risk factors for DSP were performed for DSP cases.
Results: We identified 31/137 (22.6%) HIV+ and 21/177 (11.9%) HIV− DSP cases. DSP prevalence did not differ by urbanicity, although rural participants were significantly more likely to have one asymptomatic DSP sign. Low dietary diversity, history of syphilis, history of tuberculosis, and prior metronidazole and ciprofloxacin use were associated with DSP amongst HIV+ cases, while age and education were associated with DSP in HIV− participants (all p-values $< 0{\cdot}05$). In a multivariate logistic regression model, HIV ($p = 0{\cdot}0001$) and age ($p < 0{\cdot}0001$), and ciprofloxacin exposure ($p = 0{\cdot}01$) remained independently associated with DSP. While diabetes was rare, supoptimal micronutrients levels were common among DSP cases regardless of HIV status.
Conclusions: While HIV infection is strongly associated with DSP in Zambia, history of non-ART drug exposures and low dietary diversity are also important determinants of DSP in HIV+ individuals. Treatable micronutrient deficiencies were common.

1. Introduction

Research to date on distal symmetric polyneuropathies (DSP) in sub-Saharan Africa (SSA) has focused primarily on HIV−associated DSP or toxic antiretroviral (ART) neuropathies, but the background prevalence and characteristics of DSP outside of this context is unknown. Nutritional deficiencies and other toxic exposures including treatments for common endemic infectious diseases may also be important risk factors for DSP in SSA, particularly among HIV+ individuals. Prior DSP studies have only rarely evaluated nutritional factors and often exclude persons with pre-existing risk factors other than HIV. As a consequence, there is limited understanding of the neuroepidemiological features of DSP in the region. Several studies in HIV+ populations have reported associations between DSP and food insecurity and poverty, suggesting that nutrition or environmental exposures might be important and potentially modifiable DSP risk factors [1–3]. Rural populations relying on subsistence agriculture may be especially susceptible to seasonal diet variations and food shortages compared to urban populations, but research in SSA is conducted almost exclusively in urban settings. We sought to characterize the role of urbanicity, nutritional characteristics, and non-ART neurotoxic medication exposures on the presence of DSP in Zambia, and we enriched our study with HIV+ participants to

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facilitate evaluation of the impact of HIV as well.

2. Methods

2.1. Study design and population

We conducted an observational, cross-sectional study of voluntary counseling and testing (VCT) and ART clinic attendees at two health centres in Zambia. Kamwala Health Centre is a government health centre located in the capital city, Lusaka, and serves a population of approximately 117,000 residents. Chikankata Hospital is a faith-based hospital and outpatient centre located 31 km off the main tarmac road about 125 km south of Lusaka. Chikankata serves approximately 50,000 persons, most of whom are subsistence farmers. Clinic staff were encouraged daily to refer all VCT clinic attendees with documentation of HIV serostatus and all HIV+ treatment-naïve ART clinic attendees for study eligibility assessment by research staff. However, due to low rates of identification of ART-naïve participants at the rural site during the study period, this criterion was expanded to include ART-treated HIV+ individuals without a history of dideoxynucleoside reverse transcriptase inhibitor exposure. All study participants were aged 18 or older. Exclusion criteria included inability to provide informed consent, severe leg edema or amputation, and pregnancy. Enrollment occurred from 22 April 2014 through 21 August 2014. All participants provided written informed consent. The University of Zambia Biomedical Research Ethics Committee and Michigan State University Biomedical Institutional Review Board approved the study.

2.2. Procedures

Participants were interviewed by local research personnel in the participants' preferred language between Bemba, English, Nyanja, or Tonga. Research personnel from both sites trained together at a one-day session to limit inter-site variability in interview assessments. A structured questionnaire (Appendix A) was delivered orally and captured sociodemographic and other characteristics including frequency of alcohol consumption. Food security was ascertained utilizing a survey previously employed in rural Zambia regarding: 1) taking fewer daily meals in the dry season; 2) going all day without eating in the past week, and 3) skipping one or more meals in the last week due to lack of food [1].If participants answered in the affirmative to two or more questions, they were classified as belonging to a food insecure household. Dietary diversity was assessed via the proportion of average household daily dietary energy intake in kilocalories (kcal) from maize flour, a staple food accounting for approximately two thirds of total dietary energy needs among Zambians [4]. Adult equivalent units (AEU) were calculated as one AEU for each adult and 0·7 AEU for each child in the participant's household. We classified a household as having low dietary diversity if maize flour consumption in the household exceeded 70% of total daily energy requirements (2100 kcal) per AEU per day [5]. Anthropometric measurements were also recorded. A chart abstraction tool was used to collect past medical history and prescribing information including details of specific neurotoxic drug exposures (Appendix B). However, few participants presented with medical files and participant recall was then relied upon instead. The proportion of participants with available medical files did not differ between participants with DSP (n = 12; 23.1%) and those without DSP (n = 40; 15.4%) ($p < 0.312$). For HIV+ participants, we documented time since HIV diagnosis and ART initiation, CD4 cell count within 6 months from the date of study enrollment, and hepatitis B antigen results. Hepatitis C testing was not available, but prevalence has been reported at < 1.2% among HIV+ Zambians [6].

2.3. Primary outcomes

2.3.1. DSP diagnosis and clinical case definitions

Due to lack of data regarding DSP phenotypes in SSA, we utilized a comprehensive definition for DSP diagnosis incorporating a combination of neuropathic symptoms, physical exam signs, and NCS findings defined by the American Academy of Neurology Clinical Case Definition (AAN CCD) for DSP [7]. Table 2 (found under results) provides a list of allowed DSP case definitions as well as the frequency (%) of the case definitions observed by urbanicity. We also report the prevalence of having one abnormal bilateral distal neurologic exam sign (mild vibratory loss or decreased/absent Achilles reflexes relative to patellar reflexes) in the absence of symptoms, termed one asymptomatic DSP sign, to allow comparisons to prior HIV neuropathy studies.

All study participants were examined by one of two study neurologists. For a two-week period, both neurologists were present at the rural site to reduce inter-site variability in exam procedures. Symptom assessments included the Single Question Neuropathy Screen (SQNS) and the Brief Peripheral Neuropathy Screen (BPNS) [8,9]. DSP signs were assessed using a structured exam (Appendix C) and the Utah Early Peripheral Neuropathy Screen (UEPNS) [10]. Although the UEPNS is infrequently used in HIV populations, we anticipated our population to have heterogeneous DSP etiologies not limited to HIV. Participants were considered to have probable DSP by the study neurologist if: 1) bilateral distal neuropathic symptoms of pain, parathesias, or numbness suggestive of DSP were present with or without one or more exam signs; or 2) neuropathic symptoms were absent but two or more abnormal distal bilateral neurologic exam signs were present. All participants with probable DSP were referred for nerve conduction studies to provide objective evidence for DSP diagnosis and evaluate for potential mimics.

2.4. Secondary outcomes

2.4.1. Electrophysiological and laboratory assessments

NCS were performed using the simplified protocol outlined by the AAN CCD [7]. Challenges in obtaining NCS were disproportionately encountered at the rural site due to frequent electrical outages and interferences as a result of electrical grid maintenance during study recruitment, but ultimately this only limited diagnosis in two probable DSP cases, both of which were subsequently excluded from analysis of factors associated with DSP. NCS procedures and detailed results are available as supplementary material (Appendix D). Probable DSP cases were also asked to provide a blood sample for complete blood count, blood urea nitrogen, creatinine, alanine and aspartate transaminases, thyroid stimulating hormone, free thyroxine, serum and erythrocyte folate, glycated hemoglobin (HbA1c), serum vitamin B12, and Rapid Plasmin Reagin (RPR). HbA1c was categorized as normal (< 5.7%), impaired glucose tolerance (5.7–6.4%), or diabetes (≥6.5%). Serum vitamin B12 levels were defined as low if < 200 pg/mL and borderline low if 200–300 pg/mL [11]. Low folate and borderline low folate were defined as < 3 ng/mL and 3–5.9 ng/mL, respectively. Erythrocyte folate level was considered low if < 100 ng/mL [12].

3. Statistical analysis

Extrapolating from prior studies of neuropathy prevalence in SSA, a minimum sample size of 125 HIV+ and 125 HIV− participants was anticipated to provide 98% power to detect a prevalence difference of 20% between groups, using a chi-square test with 5% significance level. Frequencies of clinical, electrodiagnostic, and laboratory findings are reported for DSP cases. All statistical analyses were carried out using SPSS version 22.0. Demographic, medical and nutritional characteristics stratified by urbanicity and HIV status and were compared using two-tailed Chi-square test for categorical variables, Student's *t*-tests for comparison of means, or a nonparametric equivalent. A two-tailed *p*-