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Malnutrition Associated With Increased Risk of Peripheral Neuropathy in Peruvian Children With HIV Infection

Peggy Martínez Esteban, MD[*], **Ton G. Thahn, PhD**[†], **Julio Flores Bravo, MD**[‡], **Lenka Kolevic Roca, MD, MPH**[§], **Nicanor Mori Quispe, MD**[‖], **Silvia M. Montano, MD, MPH**[¶], and **Joseph R. Zunt, MD, MPH**[#]

[*]Department of Neurophysiology, Instituto Especializado en Ciencias Neurològicas, Lima, Perú

[†]Department of Neurology, University of Washington, Seattle, WA

[‡]Department of Neuropediatrics, Instituto Nacional de Salud del Niño Lima, Peru

[§]Department of Infectious Diseases, Instituto Nacional de Salud del Niño Lima, Peru

[‖]Universidad Nacional Mayor de San Marcos

[¶]U.S. Naval Medical Research Center, Detachment, Lima, Perú

[#]Departments of Neurology and Global Health, University of Washington, Seattle, WA

To the Editors

In Peru, HIV infection is increasingly more frequent in women, adolescents, and children, with approximately 2% of reported AIDS cases occurring in children aged 0–14.[1,2] Although the incidence of many neurologic complications has decreased in the era of highly active antiretroviral therapy (HAART), because children now live longer, they are at higher risk of developing neurologic complications over their lifetimes.[3,4] Distal symmetric polyneuropathy (DSPN) is the most common neurologic complication of HIV infection, occurs in adults and children and can be due to HIV infection or a side effect of anti-retroviral therapy (ART)—particularly the nucleoside transcriptase inhibitors, such as didanosine, zalcitabine, and stavudine.[5,6]

The aim of this study was to determine the prevalence and correlates of DSPN in HIV-infected children in Lima, Peru. We enrolled 90 HIV-positive children and adolescents between ages 18 months and 18 years, without history of hereditary polyneuropathy or opportunistic infection associated with HIV infection after obtaining informed consent from parents or guardians and assent from children over 7 years of age. All subjects underwent a detailed neurologic examination and structured interview to detect neuropathy symptoms. Nutritional status was determined using the Water-low classification to group children into 2 indexes: weight for height and height for age, following standard National Center for Health Statistics growth tables.[7]

Neuroconduction testing was performed on the sural and peroneal nerve of all subjects using an Oxford-Teca 4-channel Synergy II; results of amplitude, latency, and conduction velocity were compared with normalized values for age.[8] The combination of neuropathic symptoms, neurologic examination, and neuroconduction testing was used to determine likelihood of

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DSPN, according to the consensus criteria recommended by the American Academy of Neurology and American Academy of Electrodiagnostic Medicine.[9] Clinical histories were reviewed to determine method and date of HIV acquisition, most recent CD4 count, viral load, and clinical status of the patient (using Center for Disease Control and Prevention HIV Classification) and any prior history, testing, and treatment of peripheral neuropathy.[10]

Of the 90 HIV-infected children enrolled, the majority (93.3%) had acquired HIV infection via vertical transmission. Average age was 7.5 years (SD ± 3.9, range 18 months to 18 years) and 43 (47.8%) were men (Table 1). Of the 64 children able to answer questions about neuropathy symptoms, 4 (67%) of 6 children with DSPN endorsed neuropathic symptoms: paresthesia (2 children), and both paresthesia and dysesthesia (2 children). On examination, 9 (75%) of the 12 children with DSPN had hyporeflexia or arreflexia at the Achilles tendon and 3 (25%) had distal paresthesia or weakness. Electrodiagnostic evidence of DSPN was present in 12 children (13.3%), 6 in children under 5 years of age. Compared with children without DSPN, children with DSPN had significantly higher viral load, lower sural nerve velocity and amplitude, and lower peroneal nerve velocity. Chronic malnutrition was more common in children with DSPN than in those without DSPN.

Nine of the 12 children with DSPN were taking HAART in the following combinations: zidovudine, lamivudine, and nelfinavir (6 children); stavudine, lamivudine, and nelfinavir (2 children); and ritonavir, lopinavir, efavirenz, and abacabir (1 child). Use of HAART was not associated with DSPN (odds ratio = 0.7; 95% confidence interval 0.1–3.9), and no significant association was detected between DSPN and any individual ART. In multivariate analysis, malnutrition was associated with higher risk for DSPN, even after adjusting for viral load and age (OR = 13.5; 95% confidence interval 1.3–146.5).

This study detected DSPN in 12 (13.3%) of 90 HIV-infected Peruvian children; this is similar to the 14% prevalence previously reported in 50 HIV-infected children in the United States, but less than the 34% reported in 39 Brazilian HIV-infected children.[11,12] The higher prevalence reported in the Brazilian study may be partially explained by their case definition; if children with both symptoms and electromography evidence of DSPN in the lower limbs are included, then only 18% (7 of 39) met criteria for DSPN. Our study used diagnostic criteria recommended by AAN and AAEM experts, and included a combination of symptoms, neurologic examination, and electrophysiologic criteria to provide a more specific diagnosis of DSPN.[9]

Our study is the first to report an association between malnutrition and DSPN in HIV-infected children. Although malnutrition was common in all children enrolled in this study, malnutrition was significantly associated with DSPN after adjusting for age and viral load. Malnutrition has been associated with lower $CD4^+$ lymphocyte counts, but we are not aware of any published report of an association between malnutrition and neurologic complications of HIV infection in children.[13]

A previous study detected an association between lower $CD4^+$ lymphocyte count and higher risk for developing dementia and DSPN.[14] When we included all children with DSPN in our analysis, we did not detect a significant difference in $CD4^+$ lymphocyte count between children with and without DSPN. However, all children with DSPN had acquired HIV infection via vertical transmission and all HIV-positive children under 5 with DSPN had advanced stages of HIV infection, suggesting that longer duration of infection may be associated with higher risk for DSPN and that risk factors for DSPN could differ for younger children.

Our study has several limitations: (1) the lack of standardized values for electrodiagnostic testing in children living in resource-poor settings makes diagnostic criteria for DSPN less

certain; (2) we did not measure for other potential causes of growth retardation that could confound our interpretation of malnutrition, such as endocrinologic or metabolic abnormalities associated with HIV infection; and (3) we used subjects' medical charts to determine if other potential causes of neuropathy were present, which could have overestimated the percentage of DSPN due to HIV infection.

In summary, DSPN was a frequent neurologic complication in HIV-infected children and was significantly associated with malnutrition. Future studies with larger numbers of children could define additional factors or micronutrient deficiencies associated with the development of DSPN, could determine if risk factors for DSPN vary by age, and could assess the benefits of reintroducing adequate nutrition upon DSPN.

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References

1. Global HIV/AIDS estimatesd—looking beyond the numbers. Lancet. 2007; 370:1802.
2. Situaciòn del VIH/SIDA. Boletín mensual de la DGE del Ministerio de Salud. Direcciòn General de Epidemiología, Ministerio de Salud; Octubre. 2006
3. Mintz M. Neurological and developmental problems in pediatric HIV infection. J Nutr. 1996; 126(10 Suppl):S3266–S3267.
4. McArthur JC, Brew BJ, Nath A. Neurological complications of HIV infection. Lancet Neurol. 2005; 4:543–555. [PubMed: 16109361]
5. Cornblath DR, Hoke A. Recent advances in HIV neuropathy. Curr Opin Neurol. 2006; 19:446–450. [PubMed: 16969153]
6. Pettersen JA, Jones G, Worthington C, et al. Sensory neuropathy in human immunodeficiency virus/acquired immunodeficiency syndrome patients: protease inhibitor-mediated neurotoxicity. Ann Neurol. 2006; 59:816–824. [PubMed: 16634006]
7. Waterlow JC, Buzina R, Keller W, et al. The presentation and use of height and weight data for comparing the nutritional status of groups of children under the age of 10 years. Bull World Health Organ. 1977; 55:489–498. [PubMed: 304391]
8. Preston, DC.; Shapiro, BE. Electromyography and Neuromuscular Disorders: Clinical Electrophysiologic Correlations. 2. Boston, MA: Butterworth-Heinemann; 2005. Approach to pediatric electromyography.
9. England JD, Gronseth GS, Franklin G, et al. Distal symmetric polyneuropathy: a definition for clinical research: report of the American Academy of Neurology, the American Association of Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology. 2005; 64:199–207. [PubMed: 15668414]
10. Centers for Disease Control and Prevention. External Review of CDC's HIV Prevention Strategies. CDC Advisory Committee on the Prevention of HIV Infection, Subcommittee on Promoting Knowledge of Serostatus; 1994.
11. Floeter MK, Civitello LA, Everett CR, et al. Peripheral neuropathy in children with HIV infection. Neurology. 1997; 49:207–212. [PubMed: 9222192]
12. Araujo AP, Nascimento OJ, Garcia OS. Distal sensory polyneuropathy in a cohort of HIV-infected children over five years of age. Pediatrics. 2000; 106:E35. [PubMed: 10969119]
13. Bachou H, Tylleskar T, Downing R, et al. Severe malnutrition with and without HIV-1 infection in hospitalised children in Kampala, Uganda: differences in clinical features, haematological findings and $CD4^+$ cell counts. Nutr J. 2006; 5:27. [PubMed: 17042940]

14. Childs EAL, Selnes OA, Chen B, et al. Plasma viral load and CD4 lymphocytes predict HIV-associated dementia and sensory neuropathy. Neurology. 1999; 52:7. [PubMed: 9921838]

TABLE 1

Demographic and Clinical Characteristics of HIV-Positive Children, by Presence of DSPN

Characteristic	DSPN (n = 12)		No DSPN (n = 78)		*P**
Age in years, mean (SD)	6.8	(5.2)	7.6	(3.7)	0.49
Male sex, n (%)	7	(58.3)	26	(46.2)	0.54
Height in centimeters, mean (SD)	64.2	(49.3)	52.1	(55.3)	0.47
Weight in kilograms, mean (SD)	24.7	(20.2)	24.3	(10.0)	0.91
Antiviral treatment, n (%)	9	(75.0)	67	(85.9)	0.04
CD4 count, mean (SD)	648.9	(352.8)	707.7	(405.2)	0.64
Viral load × 10^4, mean (SD)	13.7	(22.9)	4.8	(9.5)	0.02
Duration of infection in years mean (SD)	6.8	(5.2)	7.2	(3.8)	0.71
Route of infection, n (%)					
Vertical	12	(100.0)	72	(92.3)	1.00
Transfusion	0	(0.0)	3	(3.9)	
Sexual	0	(0.0)	1	(1.3)	
Undetermined	0	(0.0)	2	(2.6)	
Stages of infection, n (%)					
N1–Nonsymptomatic stage 1	0	(0.0)	1	(1.3)	0.80
A2–Mildly symptomatic stage 2	0	(0.0)	3	(3.9)	
B2–Moderately symptomatic stage 2	2	(16.7)	12	(15.4)	
B3–Moderately symptomatic stage 3	1	(8.3)	12	(15.4)	
C1–Severely symptomatic stage 1	0	(0.0)	1	(1.3)	
C2–Severely symptomatic stage 2	2	(16.7)	5	(6.4)	
C3–Severely symptomatic stage 3	7	(58.3)	44	(56.4)	
Severe stage of infection, n (%)	9	(75.0)	50	(64.1)	
Nutritional states, n (%)					
Normal or overweight	2	(16.7)	30	(39.0)	0.29
Chronic malnutrition	10	(83.3)	46	(59.8)	
Acute malnutrition	0	(0.0)	1	(1.3)	
Malnutrition†, n (%)	10	(83.3)	47	(61.0)	0.13
Sural nerve velocity, m/s (SD)	45.0	(5.1)	54.8	(7.9)	<0.001
Sural nerve amplitude, μV (SD)	15.1	(3.9)	28.9	(8.4)	<0.001

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Characteristic	DSPN (n = 12)		No DSPN (n = 78)		*P**
Peroneal nerve velocity, m/s (SD)	44.8	(5.2)	49.4	(4.0)	<0.001
Peroneal nerve amplitude, μV (SD)	3.8	(1.6)	4.3	(1.2)	0.24