Distal Sensory Polyneuropathy in a Cohort of HIV-Infected Children Over Five Years of Age

Alexandra Prufer de Q. C. Araújo, MD*; Osvaldo J. M. Nascimento, MD‡; and Orlando S. Garcia, MD*

ABSTRACT. *Background.* **Peripheral neuropathy in children with human immunodeficiency virus (HIV) infection has not been systematically studied.**

Objectives. **To describe the symptoms and signs of peripheral neuropathy in HIV-infected children and to determine their frequency.**

Methods. **A cross-sectional study was conducted on a convenience sample from a cohort of children older than 5 years of age at the pediatric HIV outpatient clinic of the Federal University of Rio de Janeiro. Those patients were interviewed and examined systematically for peripheral nerve symptoms and signs.**

Results. **A total of 39 patients were clinically evaluated. Their ages ranged from 5 to 14 years, and 13 patients (34%) had symptoms and signs of peripheral nerve involvement. Distal paresthesia and/or pain plus diminished ankle jerks and/or diminished vibration sense were the most common clinical findings. Symptoms were chronic and fluctuating, and pain was, in general, not severe. Nerve conduction studies primarily revealed axonal changes.**

Conclusions. **Peripheral neuropathy occurs in one third of HIV-infected children, and, in general, has less severe features than the distal sensory polyneuropathy described in adults.** ***Pediatrics*** **2000;106(3). URL: http://www.pediatrics.org/cgi/content/full/106/3/e35;** ***peripheral neuropathy, human immunodeficiency virus, children.***

ABBREVIATIONS. HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; CDC, Centers for Disease Control and Prevention; ddI, dideoxyinosine.

Worldwide, children are still becoming infected with the human immunodeficiency virus (HIV).[1] Although pediatric acquired immunodeficiency syndrome (AIDS) cases have been reported since 1983[2,3] and, soon after, many authors started to highlight the central nervous system involvement in the course of the disease,[4,5] little is known concerning these patients' peripheral nervous system status.[6,7]

Peripheral neuropathy is common in HIV-infected adults,[8–10] either related to the disease or to its treatment. It may present as inflammatory demyelinating polyneuropathy, mononeuropathy, mononeuritis multiplex, polyradiculopathy, subclinical neuropathy, or, more frequently, as distal sensory polyneuropathy.

In 1991, Raphael et al[6] reported the case of a 5-year-old boy with AIDS who had developed an inflammatory demyelinating polyneuropathy. In 1997, Floeter et al[7] described the electrophysiologic data of 50 HIV-infected patients under 18 years of age referred for evaluation of suspected neuropathy. A variety of abnormalities were described, including a probable distal sensory axonal neuropathy in 7 of the oldest children. Although biased by referral, this study suggested that at least some children eventually do develop peripheral neuropathy.

The epidemiology of HIV infection is evolving. More children are becoming infected, and attributable to better management strategies, they are surviving longer. The paucity of reports on peripheral neuropathy in HIV-infected children may reflect age-related differences in regenerative capacity or simply the underrecognition of this condition in this population. Our study was conducted to shed light on those questions.

METHODS

A clinical interview and neurologic examination were both performed by one of the authors (A.P.Q.C.A.) on all HIV-infected children older than 5 years of age from a HIV pediatric cohort followed in 1997 at the Institute of Pediatrics of the Federal University Rio de Janeiro, as part of a prospective study. The baseline neurologic evaluation is presented and did not necessarily correspond to the beginning of the clinical features. Verbal ability, which is needed to disclose the presence of subjective symptoms and to make the neurologic examination more reliable, was the reason for selection of this age group. This study was approved by the Review Board of the Institute of Pediatrics of the Federal University Rio de Janeiro, and written and informed consent was obtained from parents or legal guardians.

A structured questionnaire was used to obtain information from the patient regarding symptoms of pain, paresthesia, or weakness. Additional data on developmental milestones and a family history for peripheral neuropathies were obtained from the caretaker.

The physical examination included weight, height, head circumference, higher functions (speech, memory, and attention), cranial nerves, muscular tone, proximal (shoulder abduction and knee extension) and distal (finger extension and big-toe dorsiflexion) strength (using the Medical Research Council scale[11]), tendon reflexes, plantar response, abdominal reflexes, coordination, light touch, pain, temperature, vibration sense (with a 128-counts/second tuning fork), and blood pressure in the recumbent and standing position.

The medical charts were reviewed for route of acquisition of HIV infection, treatment with neurotoxic drugs, and disease classification (according to the Centers for Disease Control and Prevention [CDC] in 1994[12]).

Nerve conduction studies were performed using a Medelec/

From the *Federal University of Rio de Janeiro, Rio de Janeiro, Brazil; and the ‡Federal Fluminense University, Niteroi City, Brazil.

Received for publication Dec 3, 1999; accepted Apr 11, 2000.

Address correspondence to Alexandra Prufer de Q. C. Araújo, MD, Rua Gildásio Amado 55/211, Rio de Janeiro, 22631-020, Brazil. E-mail: alexprufer@hotmail.com

TECA Sapphire 2-channel model electromyograph (Medelec, Manor Way, Old Woking, Surrey, England) at a room temperature of 22°C. Median, ulnar, peroneal, and sural nerves on the right side were examined. Miniature bipolar stimulator and recording electrodes were appropriate for pediatric use. A constant current stimulation with duration of 100 microseconds was delivered at 1 pulse/second. Compound muscle action potentials were recorded on the abductor pollicis brevis and extensor digitorum brevis using the belly-tendon configuration, with an orthodromic stimulus. F response was looked for on the peroneal nerve after 20 successive supramaximal stimulations. Sensory nerve action potentials were recorded using an antidromic stimulus. Amplitudes, latencies, and conduction velocities were considered abnormal if outside the range of medium ± 2 standard deviation of the normal age-matched values of this laboratory. The selection of children in our study, based on age, diminished the variability that could have been found in conduction studies if younger children had been included.[13] All patients included in the clinical study were also referred for nerve conduction studies.

The patient was considered to have peripheral neuropathy if presenting simultaneously at least 1 symptom (distal pain, paresthesia, hypoesthesia, or weakness) and 1 sign (amyotrophy, hypotonia, weakness, diminished deep tendon reflexes, hypoesthesia, or postural hypotension). Encephalopathy was diagnosed when 1 or more of the following features were present: microcephaly, developmental delay, pyramidal signs, and higher function disorder. A simplification of the HIV-1-associated progressive encephalopathy published guidelines[14] at the time of the study was adopted because of operational issues. Neurotoxic drug exposure was considered if symptoms developed while taking one of the following drugs: dideoxyinosine (ddI), dideoxycytidine, or isoniazid. Disease duration was considered the difference of the date of transfusion to the date of the evaluation if this route, and the same as the age of the patient who had acquired it if transmission had been vertical or undetermined.

There was no attempt, in the present study, to quantify the clinical features, relying either on visual analog scales or on sensory thresholds. These children were not submitted to lumbar puncture or nerve biopsy because of ethical issues.

RESULTS

From the total of 128 patients followed at the HIV pediatric clinic in 1997, 55 were 5 years old or older. During the study, 6 children died, 2 moved to other cities, and 8 did not attend their consultations regularly; therefore, 39 were included in the present study. Their ages ranged from 5 to 14 years old (mean: 8.4). There was a similar distribution in gender (21 males). Most of them had acquired the infection from their mothers (77%), 4 by transfusion (from birth up to 5 years old), and in 5 the route of acquisition could not be determined.

Symptoms related to peripheral nerve dysfunction were found in 22 of 39 children (56%). Pain was the complaint of 13 patients, predominantly distal in the lower limbs. Pain was described as burning in some or as evoked related to walking a longer distance in others. Paresthesia was reported in 15 children, located distally in upper and lower limbs. Those symptoms, although long-lived, did not interfere in daily activities and had a fluctuating course. They had not been described to the pediatricians in previous medical visits, although the symptoms had been present for >1 year in more than one half of those patients.

Neurologic evaluation depicted peripheral nerve abnormalities in 19 patients (49%). Diminished distal vibration sense (10/39) and diminished or abolished tendon reflexes (11/39) were the most common clinical findings. Hypotonia (4/39), distal muscle weakness (3/39), and diminished distal tactile sensation (1/39) were also observed.

This population, based on clinical findings, could be divided into 4 groups: with symptoms, signs, both, or neither. A total of 13 children (34%) had symptoms and signs of peripheral neuropathy. In 8 of the 13 patients, the use of potential neurotoxic drugs was absent before the beginning of the clinical features related to the peripheral nervous system (Table 1). In the remaining 5 patients, the clinical features developed after having been on potential neurotoxic agents (Table 1). Of the 26 children without peripheral neuropathy, 21 were using a combination of antiretroviral drugs that included ddI.

Nine of the 13 children with symptoms and signs were submitted to nerve conduction studies. Denial of consent was the primary reason for not performing the test. The sural nerve was the one most commonly involved, with either low amplitudes or small alterations in conduction velocities or latencies (Table 1). The other common finding was the absence of F response in the peroneal nerve. No conduction block was observed in the studied nerves. In 7 children, the abnormalities occurred in >1 nerve.

Disease duration, presence of undernourishment, or degree of immunodeficiency was not associated with the presence of peripheral neuropathy. Although nonsignificant, peripheral neuropathy had a higher prevalence ratio in the group of children with encephalopathy (1.53; 95% confidence interval: .86–3.4), as well as in those with symptomatic AIDS (1.42; 95% confidence interval: .46–4.53).

DISCUSSION

Peripheral neuropathy occurs in children with AIDS. In this convenience sample of 39 children over 5 years of age, symptoms and signs related to peripheral nerve involvement are present in one third of the cases. The same prevalence has been found in reports of adults with AIDS[9] but few references of clinical features of peripheral neuropathy had been described in pediatric neurologic series.[4–7] One could explain the lack of peripheral neuropathy in studies of the beginning of the epidemics on the ground of the early mortality of those children. Dying before acquiring adequate language skills would preclude symptoms such as paresthesia or pain from being confirmed. Furthermore, the high prevalence of encephalopathy, with its florid clinical picture in this population, could overshadow the less striking features of peripheral neuropathy.

The predominance of chronic sensory complaints, pain, and paresthesia, bilaterally and distally located, is similar to what has been found in adult series.[8,9] Nevertheless, in children those symptoms are not severe and they are not referred to their clinicians spontaneously. The findings of diminished ankle jerks and vibration sense are also found in adults.[8,9] Relying on clinical aspects, one could consider those clinical features attributable to possible HIV-associated predominantly sensory polyneuropathy.[14] There was no attempt, in the present study, to quantify the clinical features, relying on visual analog scales or on sensory thresholds.

It is important to notice that pain, described as burning in the feet that may interfere with walking

TABLE 1. Clinical and Nerve Conduction Features of Patients With Peripheral Neuropathy

Age (Years)	Drug Exposure	CD4	Symptoms/Signs	Nerve Conduction
7	ZDV	32%	Pain and paresthesia in feet Brisk reflexes except in the ankle	Abnormal in upper limb (sensory latency 2.64 ms [102.2% UNL]) And lower limb (sensory latency 3.06 ms [103.4% UNL]; sensory NCV 41.9 m/s [97.6% LNL])
8	ZDV	13%	Pain in feet ↓ vibration sense up to the ankles	Abnormal in lower limb (sensory latency 3.44 ms [116.2% UNL]; sensory NCV 35.8 m/s [83.4% LNL] and NE F response)
5	—	27%	Pain in feet Hypotonia and ↓ tendon reflexes	Abnormal in upper limb (sensory latency 2.63 ms [101.8% UNL]) and lower limb (NE H reflex)
5	ZDV	9%	Pain in feet, paresthesia in upper and lower limbs Hypotonia	Abnormal in upper limb (motor NCV 46.6 m/s [95.6% LNL]; sensory NCV 48.3 m/s [98.4% LNL])
7	ZDV	9%	Pain in feet Diffuse hypotonia ↓ ankle reflexes	ND
7	ZDV	12%	Pain in feet Diffuse hypotonia ↓ ankle reflexes	Abnormal in lower limb (NE F response)
13	ZDV	1%	Pain, paresthesia and hypoesthesia in hands and feet ↓ reflexes in lower limbs ↓ tactile and vibration Sense in hands and feet	Abnormal in lower limb (NE F response)
12	ZDV	23%	Paresthesia in hands and feet ↓ ankle reflexes	ND
9	ZDV ddI (1 m)	15%	Pain in lower limb ↓ vibration sense up to the ankles	Abnormal in upper limb (sensory latency 3.17 ms [122.7% UNL]; proximal motor amplitude 5.23 mV [87.0% LNL/R 5.0%])
14	ZDV ddI (15 m) INH	3%	Pain and paresthesia in hands and feet ↓ vibration sense up to the ankles and wrists	ND
5	ZDV ddI (6 m)	19%	Paresthesia in hands and feet ↓ vibration sense up to the ankles ↓ ankle reflexes	Abnormal in lower limb (sensory latency 3.17 ms [107.0% UNL]; sensory amplitude 17.3 μV [98.9% LNL]; sensory NCV 42.5 m/s [99.0% LNL]; NE proximal motor amplitude and F response)
8	ZDV ddI (3 m)	20%	Paresthesia in right foot ↓ vibration sense up to the ankles	Abnormal in lower limb (sensory amplitude 16.4 μV [93.7% LNL]; sensory latency 3.08 ms [104.0% UNL]; NE F response)
7	ZDV ddI (20 m)	28%	Paresthesia in right hand ↓ vibration sense up to the ankles and wrists ↓ ankle reflexes	ND

ND indicates not done; UNL, upper normal limit; NCV, nerve conduction velocity; LNL, lower normal limit; ↓, diminished; NE, nonevocable; R, percentual ratio of proximal/distal amplitude; ZDV, zidovudine; INH, isoniazid.

function, even with a normal peripheral nerve examination, might be attributable to neuropathy with small fiber involvement. In the present study, we found 3 children with those features. Neuropathies with predominantly small fiber involvement are notoriously difficult to diagnose because the conventional neurological examination and the nerve conduction tests are usually normal. Recently, skin biopsy has been developed as a technique useful for detecting the involvement of small unmyelinated fibers in sensory neuropathies.[15] The intraepidermal nerve fiber density in sections of skin, obtained by punch skin biopsy, could potentially diagnose this condition even in children.[16] The density of the nerve fibers may estimate neuropathy severity and would probably be the measurement of choice in the setting of HIV-associated peripheral neuropathy in children. Ethical issues, a previous obstacle for such an invasive procedure, will certainly weaken, justifying its use in future studies.

The nerve conduction studies, performed in 9 of the 13 patients with clinical features of peripheral neuropathy in the present study, confirmed the peripheral nerve involvement and indicated its axonal predominance. Low amplitudes of sural nerve potentials with relative preserved conduction velocities were the most common abnormality in a previous larger nerve conduction study.[7] Unfortunately, a comparison of the absolute results was not possible because of the lack of those values in this previous study.[7] We also found the sural nerve to be one of the most commonly involved nerve.

According to the current case definition for clinical diagnosis of HIV-associated peripheral nervous system disorders,[14] the 13 children described in the present study fulfill 3 of 5 criteria of probable HIV-

associated predominantly sensory polyneuropathy. In 8 of the children, the clinical features, primarily the symptoms, had begun before the exposure to neurotoxic drugs, which meets another requirement. Although sensory clinical signs could be thought to be unreliable, they stand as 2 of the 5 criteria used for the definition of HIV-1–associated predominantly sensory polyneuropathy.[14] Indeed, it has been shown that even a screening examination performed by trained nonphysicians[17] is sensitive, compared with a detailed examination by a neurologist.

Many risk factors have been listed for the peripheral neuropathy found in adults with AIDS.[9,10,18,19] A small trend of a higher prevalence for peripheral neuropathy occurring in children with encephalopathy or symptomatic AIDS (CDC classifications B and C) is shown in this study. However, none of the factors presently studied had a significant correlation with the presence of symptoms and signs of peripheral neuropathy in these children, which might have been attributable to a type 2 error. Therefore, larger series as well as prospective studies would be more appropriate to define the true risk factors for the development of this disorder and should be conducted in this age group as well.

CONCLUSION

This study shows that peripheral neuropathy does occur in children with AIDS, indicating a prevalence rate of 34% of a possible predominantly sensory polyneuropathy. Our data, however, point to a less severe clinical picture than the one found in adults. More attention to symptoms and signs in the follow-up of pediatric patients with HIV is needed, particularly now, with a longer life expectancy. Management measures to avoid more harm to the peripheral nervous system, to relieve those children from uncomfortable symptoms, and to try to protect them from developing walking disabilities need to be adopted.

ACKNOWLEDGMENT

We thank Dr Justin C. McArthur at Johns Hopkins University School of Medicine for his helpful comments.

REFERENCES

1. Joint United Nations Program on HIV/AIDS World Health Organization (UNAIDS/WHO). *Mother to Child Transmission: Report on the Global HIV/AIDS Epidemic*. Geneva, Switzerland: Joint United Nations Program on HIV/AIDS World Health Organization (UNAIDS/WHO); 1998:48–50
2. Oleske J, Minetor A, Cooper R, et al. Immune deficiency syndrome in children. *JAMA*. 1983;249:2345–2349
3. Rubinstein A, Sicklick M, Gupta A, et al. Acquired immunodeficiency with reversed T4/T8 ratios in infants born to promiscuous and drug-addicted mothers. *JAMA*. 1983;249:2350–2356
4. Belman AL, Ultmann MH, Horoupian D, et al. Neurological complications in infants and children with acquired immune deficiency syndrome. *Ann Neurol*. 1985;18:560–566
5. Epstein LG, Sharer LR, Joshi VV, Fojas MM, Koenigsberg MR, Oleske JM. Progressive encephalopathy in children with acquired immune deficiency syndrome. *Ann Neurol*. 1985;17:488–496
6. Raphael SA, Price ML, Lischner HW, Griffin JW, Grover WD, Bagasra O. Inflammatory demyelinating polyneuropathy in a child with symptomatic human immunodeficiency virus infection. *J Pediatr*. 1991;118:242–245
7. Floeter MK, Civitello LA, Everett CR, Dambrosia J, Luciano CA. Peripheral neuropathy in children with HIV infection. *Neurology*. 1997;49:207–212
8. Cornblath DR, McArthur JC. Predominantly sensory neuropathy in patients with AIDS and AIDS-related complex. *Neurology*. 1988;38:794–796
9. So YT, Holtzman DM, Abrams DI, Olney RK. Peripheral neuropathy associated with acquired immunodeficiency. *Arch Neurol*. 1988;45:945–948
10. Simpson DM, Wolfe DE. Neuromuscular complications of HIV infection and its treatment. *AIDS*. 1991;5:917–926
11. Medical Research Council. *Aids to the Examination of the Peripheral Nervous System*. London, England: Baillière Tindall; 1986
12. Centers for Disease Control and Prevention. 1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age; official authorized addenda: human immunodeficiency virus infection codes and official guidelines for coding and reporting ICD-9CM. *MMWR CDC Surveill Summ*. 1994;43:RR–12
13. Jones HR Jr, Harmon RL, Harper CM Jr, Bolton CF. An approach to pediatric electromyography. In: Jones HR Jr, Bolton CF, Harper CM Jr, eds. *Pediatric Clinical Electromyography*. Philadelphia, PA: Lippincott-Raven; 1996:1–36
14. Working Group of the American Academy of Neurology AIDS Task Force. Nomenclature and research case definitions for neurologic manifestations of human immunodeficiency virus type-1 infection. *Neurology*. 1991;41:778–785
15. McArthur JC, Stocks EA, Hauer P, Cornblath DR, Griffin JW. Epidermal nerve fiber density: normative reference range and diagnostic efficiency. *Arch Neurol*. 1998;55:1513–1520
16. McCarthy BG, Hsieh ST, Stocks A, et al. Cutaneous innervation in sensory neuropathies: Evaluation by skin biopsy. *Neurology* 1995;45:1848–1855
17. Marra CM, Boutin P, Collier AC. Screening for distal sensory peripheral neuropathy in HIV-infected persons in research and clinical settings. *Neurology* 1998;51:1678–1681
18. Kieburtz KD, Gian DW, Schiffer RB, Vakil N. Abnormal vitamin B12 metabolism in human immunodeficiency virus infection. *Arch Neurol* 1991;48:312–314
19. Childs EA, Lyles RH, Selnes OA, et al. Plasma viral load and CD4 lymphocytes predict HIV-associated dementia and sensory neuropathy. *Neurology*. 1999;52:607–613

Distal Sensory Polyneuropathy in a Cohort of HIV-Infected Children Over Five Years of Age

Alexandra Prufer de Q. C. Araújo, Osvaldo J. M. Nascimento and Orlando S. Garcia

Pediatrics 2000;106;e35
DOI: 10.1542/peds.106.3.e35

Distal Sensory Polyneuropathy in a Cohort of HIV-Infected Children Over Five Years of Age

Alexandra Prufer de Q. C. Araújo, Osvaldo J. M. Nascimento and Orlando S. Garcia

Pediatrics 2000;106;e35
DOI: 10.1542/peds.106.3.e35