Acta Neurol. Belg., 2011, **111**, 41-44

Prevalence of peripheral neuropathy in patients with HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP)

Morteza SAEIDI, Payam SASANNEJAD, Mohsen FOROUGHIPOUR, SaeedReza SHAHAMI and Ali SHOEIBI
Mashhad University of Medical Sciences, Iran

Abstract

While the most common neurological disorder associated with Human T lymphotropic virus type-1 (HTLV-1) infection in the endemic areas is HTLV-1 associated myelopathy also know as tropical spastic paraparesis (HAM/TSP), other disorders such as optic neuropathy, peripheral neuropathy and cerebellar diseases have also been reported in patient with this infection. In this paper, we studied the prevalence of peripheral nerve involvement in patients with HAM/TSP.

Methods: Seventy three patients diagnosed with HAM/TSP in accordance to criteria set by the World Health Organization (WHO) were evaluated in this cross-sectional study. Clinical and electrodiagnostic criteria were used for the diagnosis of peripheral neuropathy.

Results: Electrodiagnostic studies showed that 30.1% of patients with HAM/TSP had peripheral nerve involvement. All patients had predominantly axonal neuropathy with sensory-motor polyneuropathy being the most common neuropathy observed in our patients.

Discussion and conclusion: Peripheral neuropathy may be more common than previously thought and should be checked systematically in all patients with HAM/TSP.

Key words: HTLV-1; HTLV-1 associated myelopathy/tropical spastic paraparesis; neuropathy.

Introduction

Human T lymphotropic virus type 1 (HTLV-1) is a retrovirus that results in adult T cell leukemia (ATL) and HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP) in humans (1-3). Despite numerous studies on CNS complications of HAM/TSP, little has been written on PNS involvement in HAM/TSP (4) and only a few cases with a limited number of patients have been published focusing on PNS complications of HAM/TSP (5-11). It is hypothesised that immune-mediated perivascular mononuclear cuffing around the vasa nervorum of peripheral nerves can cause peripheral neuropathy in HAM/TSP (11-12).

HTLV-1 infection is endemic in certain regions of the world such as south-western Japan, Central Africa, the Caribbean islands, regions of South America, Melanesia (13) and also the Khorasan Razavi province in northeast of Iran (13-15). It is estimated that about 2.3%-3% of general populations in this province is infected with the HTLV-1 virus (14, 16). In this paper, we studied the prevalence of different types of peripheral neuropathy in a large population of patients with HAM/TSP.

Methods

Seventy three patients diagnosed with HAM/TSP based on criteria set by WHO (17), were evaluated in this cross-sectional study. These patients were visited in the neurology clinic of Qaem hospital of Mashhad from October 2006 to October 2008. All positive serum samples for HTLV-1 evaluated by ELISA were also confirmed by serum PCR or western blot studies. Lumbar puncture was performed on all patients and HAM/TSP was confirmed by positive anti-HTLV-1 antibody in the cerebrospinal fluid of all patients. All patients underwent brain and cervical MRI and other causes of myelopathy were ruled out. The ethic committee of the Mashhad University of Medical Sciences approved this study and all patients signed informed consents.

Exclusion criteria included 1) co-infection with HIV, HTLV-2, syphilis, leprosy, hepatitis B, hepatitis C, brucellosis or other infections that can cause peripheral neuropathy, 2) presence of diabetes, hypothyroidism, renal failure, vitamin B12 deficiency and other known causes of peripheral neuropathy, 3) use of any drugs or medications known to cause peripheral neuropathy and lastly, 4) positive family history for peripheral neuropathy.

Four-limb electromyography and nerve conduction studies were carried out using conventional techniques. We used the following parameters: motor nerve conduction velocities (NCVs) and compound muscle action potentials (CMAPs) of median, ulnar, radial, posterior tibial and peroneal nerves; sensory nerve action potentials (SNAPs) of median, ulnar and sural nerves; F waves of median, ulnar, posterior tibial and peroneal nerves; and H reflexes. The following criteria were used for diagnosis of axonal neuropathy: (a) reduction in conduction velocity not below 70% of normal lower limit; (b) absence of partial conduction block or prolonged distal latencies more than 130% of normal values (c) CMAP amplitudes less than 70% of normal lower limit and (d) presence of spontaneous potentials (positive sharp waves, fibrillation) with reduced recruitment pattern.

Clinical data including symptoms, neurological examination findings, electrodiagnostic findings and demographic data were collected in a specific data collection sheet for each patient and were analyzed with SPSS software. Neurological disability was determined based upon Motor Disability Grading (MDG) system (1).

Results

Patients included in the study had a mean age of 45.9 ± 14.3 years (Min: 13 and Max: 71 years).

The mean duration from onset of symptoms to diagnosis was less than 10 days (new onset) in 2 patients, 11 days to 6 months (sub-acute) in 18 patients and more than 6 months (chronic) in 53 patients.

There was a positive family history for HAM/TSP in 15.1% of our patients and 36.1% of them had at least one first degree relative with a positive blood sample for anti HTLV-1 antibody. 92.9% of patients had a history of breastfeeding for more than one year, 34.2% had had at least one major surgery, 16.4% had undergone at least one dental procedure and 15.3% had a history of blood transfusion. Six of our patients were working in a hospital or clinical laboratory center.

The presenting symptoms of our patients are summarized in Table 1. Four patients had optic atrophy and 5.9% of them had unilateral sensorineural hearing loss. In 65.8% of patients limb paresthesia was present, and there was decreased temperature sensation in the distal lower limbs of 13.7% of them. 11% of patients exhibited pain perception disorders in the sensory examination of the lower limbs. 39.7% of patients had decreased vibration sensation and 28.8% of them had impaired proprioception in their lower limbs. Four patients had different sensory levels at T4, T7, T8 and T10. The mean MDG (motor disability grading) of our patients was 3.41±1.6 (Min: 1, Max: 8).

Deep tendon reflexes examination in our patients showed: decreased or absent brachioradial reflex in 1.4% of patients, decreased right patella reflex in 4.1%, decreased left patella reflex in 2.7%, decreased left ankle reflex in 6.8% and decreased or absent right ankle reflex in 5.5% of patients. Distal limb weakness in the upper and/or lower limbs was present in 13.7% of patients and 4.1% had distal muscle atrophy.

Electrodiagnostic studies showed that 30.1% of patients (22 patients) with HAM/TSP had peripheral nerve involvement (Table 2). All patients had predominantly axonal neuropathy. Only two had pure

Table 1

Presenting symptom of HAM/TSP in our study

Symptom	Frequency	Percent (%)
Lower limbs weakness	65	89
Urinary symptoms	56	76.7
Limb paresthesia	49	67.1
Fatigue	36	49.3
Low back pain	32	43.8
Diffuse limb pain	15	20.5
Decreased libido	8	11.2
Radicular pain	7	9.8
Impotence	4	5.6
Disequilibrium	1	1.4
Lower and upper limbs weakness	1	1.4

Table 2

Types of peripheral neuropathy in patients with HAM/TSP

Type	Frequency			Percent (%)
	Male	Female	Total	
Sensory motor polyneuropathy	3	14	17	77.3
Multiple mononeuropathy	1	2	3	13.6
Pure sensory polyneuropathy	1	1	2	9.1
Total	5	17	22	100

sensory involvement. The other twenty patients had mixed sensorimotor neuropathy (17 patients) and mononeuritis multiplex (3 cases).

Discussion

In a study of 335 HTLV-1 positive patients without HAM/TSP, 6.3% had a clinical or electrodiagnostic finding of predominantly sensory polyneuropathy and one patient had multiple mononeuropathy (18). Electrodiagnostic findings suggestive of peripheral neuropathy have been reported in up to 50% of patients with HAM/TSP in some studies (19) and up to 15% of these patients have been shown to have clinical findings compatible with polyneuropathy (19-20). In the present study, 26% of patients had electrodiagnostic findings of predominantly axonal polyneuropathy. There are also a few case reports of multiple mononeuropathy in patients with HAM/TSP (21). In our study, three patients (4.1%) had mononeuritis multiplex according to clinical and electrodiagnostic findings.

Patients entered into this study consisted of 24, 7% males and 75, 3% females, a finding similar with other studies emphasizing that HAM/TSP is more common in women (19). In our study, the prevalence of neuropathy was not significantly different between males and females. Interestingly, however, neuropathy was significantly less common in patients who had a history of breastfeeding for more than one year ($p = 0.03$). This suggests that breastfeeding might be a protective factor for peripheral nerve involvement in HAM/TSP (22).

Prevalence of peripheral neuropathy was significantly higher in patients who had a history of blood transfusion ($p = 0.01$), leading to the conclusion that the blood-borne transmission of HTLV-1 infection may be a risk factor for peripheral nerve involvement. The duration of disease (HAM/TSP) was not significantly correlated to the prevalence of peripheral neuropathy ($p = 0.23$), but higher scores of MDG were associated with a greater prevalence of peripheral neuropathy ($p = 0.01$).

Even though ankle and knee hypo or areflexia was observed more commonly in patients with peripheral nerve involvement in electrodiagnosis than patients without involvement, this difference was not statistically significant ($p = 0.35$). In other words, the absence of hypo or areflexia does not rule out the presence of peripheral neuropathy and similarly, the presence of hypo or areflexia does not necessarily imply the presence of neuropathy. This can be explained by the simultaneous upper and lower motor neuron involvement as well as predominantly axonal type of injury without significant demyelination in the cases of neuropathy without hypo or areflexia. The involvement of spinal roots or posterior spinal column can explain hypo or areflexia in HAM/TSP patients who do not have peripheral neuropathy.

In our study there was no statistically significant association between the presence or absence of clinical paresthesia and peripheral neuropathy in electrodiagnostic studies ($p = 0.25$). Nine of the 24 patients with no complaint of sensory problems had peripheral neuropathy in the electrodiagnostic studies. On the other hand, only 62.5% of patients with paresthesia (30 of 49 patients) had electrodiagnostic evidence of neuropathy. This can be explained by the fact that paresthesia can be the result of posterior root or posterior column involvement without any associated neuropathy.

Peripheral neuropathy was statistically related with distal muscle weakness in the motor examination ($p = 0.04$), and impaired pain ($p = 0.001$), temperature ($p = 0.04$), position ($p = 0.01$), and vibration sensation ($p = 0.02$) in the sensory examination, but not with the presence of muscle atrophy in limb inspection ($p = 0.28$). In fact, muscle atrophy in these patients can be secondary to limb disuse rather than neuropathy.

Conclusion

Despite previous beliefs that peripheral nerve involvement can be seen rarely in patients with HAM/TSP, it seems that HAM/TSP with simultane-

ous peripheral neuropathy is relatively common in endemic areas (19). In our study conducted in the endemic area of Khorasan Razavi province 30% of all patients with HAM/TSP and 67.2% of HAM/TSP patients with clinical findings suggesting peripheral neuropathy present peripheral nerve involvement in the electrodiagnostic studies. We recommend to screen systematically for peripheral neuropathy in all patients with "HAM/TSP".

REFERENCES

1. Izumo S, Umehara F, Osame M. HTLV-I-associated myelopathy. Neuropathology. 2000 Sep;20 Suppl: S65-8.
2. Osame M, Matsumoto M, Usuku K, Izumo S, Ijichi N, Amitani H. *et al*. Chronic progressive myelopathy associated with elevated antibodies to human T-lymphotropic virus type I and adult T-cell leukemialike cells. Ann Neurol. 1987 Feb;21(2):117-22.
3. Vernant JC, Maurs L, Gessain A, Barin F, Gout O, Delaporte JM. *et al*. Endemic tropical spastic paraparesis associated with human T-lymphotropic virus type I: a clinical and seroepidemiological study of 25 cases. Ann Neurol. 1987 Feb;21(2):123-30.
4. Matsui H, Udaka F, Kubori T, Oda M, Nishinaka K, Oka N. HTLV-I-associated peripheral neuropathy with smoldering-type adult T-cell leukemia. Neurologist. 2006 Mar;12(2):109-13.
5. Said G, Goulon-Goeau C, Lacroix C, Feve A, Descamps H, Fouchard M. Inflammatory lesions of peripheral nerve in a patient with human T-lymphotropic virus type I – associated myelopathy. Ann Neurol. 1988 Aug;24(2):275-7.
6. Arimura K, Rosales R, Osame M, Igata A. Clinical electrophysiologic studies of HTLV-I-associated myelopathy. Arch Neurol. 1987 Jun;44(6):609-12.
7. Akamatsu MM, Mitsui Y, Kihara M, Ohtsuka K, Takahashi M. [A case of polyneuropathy with B-CLL and HTLV-I associated myelopathy (HAM)]. Rinsho Shinkeigaku. 1997 Aug;37(8):701-3.
8. Shibasaki H, Endo C, Kuroda Y, Kakigi R, Oda K, Komine S. Clinical picture of HTLV-I associated myelopathy. J Neurol Sci. 1988 Oct;87(1):15-24.
9. Sugimura K, Takahashi A, Watanabe M, Mano K, Watanabe H. Demyelinating changes in sural nerve biopsy of patients with HTLV-I-associated myelopathy. Neurology. 1990 Aug;40(8):1263-6.
10. Bhigjee AI, Bill PL, Wiley CA, Windsor IM, Matthias DA, Amenomori T. *et al*. Peripheral nerve lesions in HTLV-I associated myelopathy (HAM/TSP). Muscle Nerve. 1993 Jan;16(1):21-6.
11. Kiwaki T, Umehara F, Arimura Y, Izumo S, Arimura K, Itoh K. *et al*. The clinical and pathological features of peripheral neuropathy accompanied with HTLV-I associated myelopathy. J Neurol Sci. 2003 Jan 15;206(1):17-21.
12. Umehara F, Izumo S, Nakagawa M, Ronquillo AT, Takahashi K, Matsumuro K. *et al*. Immunocytochemical analysis of the cellular infiltrate in the spinal cord lesions in HTLV-I-associated myelopathy. J Neuropathol Exp Neurol. 1993 Jul;52(4):424-30.
13. Gessain A, Mahieux R. [Epidemiology, origin and genetic diversity of HTLV-1 retrovirus and STLV-1 simian affiliated retrovirus]. Bull Soc Pathol Exot. 2000 Jul;93(3):163-71.
14. Shirdel A, Rafatpanah H, Rahimi H, Rezaee AR, Azarpajooh MR, Yazdi AB. *et al*. A functional polymorphism of the granulocyte macrophage colony stimulating factor is not associated with the outcome of HTLV-I infection. Iranian Journal of Basic Medical Sciences. 2010;13(2 SPRING):40-7.
15. Arjmand B, Aghayan SH, Goodarzi P, Farzanehkhah M, Mortazavi SM, Niknam MH. *et al*. Seroprevalence of human T lymphtropic virus (HTLV) among tissue donors in Iranian tissue bank. Cell and Tissue Banking. 2009;10(3):247-52.
16. Safai B, Huang JL, Boeri E, Farid R, Raafat J, Schutzer P. *et al*. Prevalence of HTLV type I infection in Iran: a serological and genetic study. AIDS Res Hum Retroviruses. 1996 Aug 10;12(12):1185-90.
17. De Castro-Costa CM, Araújo AQC, Barreto MM, Takayanagui OM, Sohler MP, Da Silva ELM. *et al*. Proposal for diagnostic criteria of tropical spastic paraparesis/HTLV-I- associated myelopathy (TSP/HAM). AIDS Research and Human Retroviruses. 2006;22(10):931-5.
18. Leite AC, Silva MT, Alamy AH, Afonso CR, Lima MA, Andrada-Serpa MJ. *et al*. Peripheral neuropathy in HTLV-I infected individuals without tropical spastic paraparesis/HTLV-I-associated myelopathy. J Neurol. 2004 Jul;251(7):877-81.
19. Grindstaff P, Gruener G. The peripheral nervous system complications of HTLV-1 myelopathy (HAM/TSP) syndromes. Semin Neurol. 2005 Sep;25(3):315-27.
20. Bhigjee AI, Kelbe C, Haribhai HC, Windsor IM, Hoffmann MH, Modi G. *et al*. Myelopathy associated with human T cell lymphotropic virus type I (HTLV-I) in natal, South Africa. A clinical and investigative study in 24 patients. Brain. 1990 Oct;113 (Pt 5):1307-20.
21. Douen AG, Pringle CE, Guberman A. Human T-cell lymphotropic virus type 1 myositis, peripheral neuropathy, and cerebral white matter lesions in the absence of spastic paraparesis. Arch Neurol. 1997 Jul;54(7):896-900.
22. Weitzmann SGM, … Kyle RA, Schiffer CA. Neoplastic diseases of blood. 2nd ed. New York Churchill Livingstone; 1991: p. 101-3.

Ali Shoeibi,
Assistant Professor of Neurology
Mashhad University of Medical Sciences, Iran
shoeibia@mums.ac.ir