Journal of NeuroVirology, 13: 260–267, 2007

ISSN: 1355-0284 print / 1538-2443 online
DOI: 10.1080/13550280701258431

informa
healthcare

Abnormalities of spinal magnetic resonance images implicate clinical variability in human T-cell lymphotropic virus type I–associated myelopathy

Fujio Umehara,[1] Hirohisa Nose,[1] Mineki Saito,[2] Michinari Fukuda,[3] Mieko Ogino,[3] Tomoko Toyota,[4] Tomoaki Yuhi,[4] Kimiyoshi Arimura,[1] and Mitsuhiro Osame[1]

[1]Department of Neurology and Geriatrics, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima, Japan. [2]Department of Microbiology, Kanazawa Medical University, Ishikawa, Japan [3]Department of Neurology, Kitazato University School of Medicine, Sagamihara, Japan [4]Department of Neurology, University of Occupational and Environmental Health, Kitakyusyu, Japan

This study investigated the role of human T-cell lymphotropic virus type I HTLV-I infection in 11 patients who developed slowly progressive myelopathy with abnormal spinal cord lesions. The authors performed clinical and neuroradiological examinations and calculated the odds that an HTLV-I–infected individual of a specific genotype, age, and provirus load has HTLV-I–associated myelopathy/tropical spastic paraparesis (HAM/TSP). Anti-HTLV-I antibodies were present in both the serum and cerebrospinal fluid in all of the patients. Abnormal magnetic resonance imaging (MRI) lesions were classified as cervical to thoracic type (CT type), cervical type (C type), and thoracic type (T type). In each type, there was swelling of the spinal cords with high-intensity lesions, which were located mainly in bilateral posterior columns, posterior horns, or lateral columns. Virological and immunological analyses revealed that all patients showed a high risk of developing HAM/TSP. These 11 patients may have developed HAM/TSP, as manifested by spinal cord abnormalities shown on MRI. These MRIs implicate clinical variability of HAM/TSP, which may indicate active-early stages of HAM/TSP lesions. *Journal of NeuroVirology* (2007) **13,** 260–267.

Keywords: HAM/TSP; HTLV-I; MRI; myelopathy; spinal cord

Introduction

Human T-cell lymphotropic virus type I (HTLV-I) is associated with adult T-cell leukemia (ATL) and a chronic progressive disease of the central nervous system (CNS) termed HTLV-I–associated myelopathy/tropical spastic paraparesis (HAM/TSP) (Osame *et al*, 1986; Gessain *et al*, 1985). The disease predominantly affects the thoracic level of the spinal cord, and manifests as atrophy of the lateral columns (Iwasaki, 1990). These lesions are associated with perivascular and parenchymal lymphocytic infiltration, with the presence of foamy macrophages, proliferation of astrocytes, and fibrillary gliosis (Umehara and Osame, 2003). Recently, several cases of HAM/TSP showing magnetic resonance imaging (MRI) abnormalities in the spinal cord have been reported (Shakudo *et al*, 1999; Watanabe *et al*, 2001; Tajima *et al*, 2003) These changes consisted of spinal cord swelling with high signal intensity and contrast enhancement at the cervical and thoracic levels. We reported four cases in which the patients developed slowly progressive elopathy with abnormal MRI lesions at the cervical cord levels, and we proposed that these four cases may be a variant form of HAM/TSP that predominantly involves the cervical spinal cord levels (Umehara *et al*, 2004).

In this paper, we describe the cases of 11 patients with progressive myelopathy with positive anti-HTLV-I antibodies in the serum and cerebrospinal

Address correspondence to Dr. Fujio Umehara, Department of Neurology and Geriatrics, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima University, Sakuragaoka 8-35-1, Kagoshima, 890-8520, Japan. E-mail: umehara@m2.kufm.kagoshima-u.ac.jp

Received 13 December 2006; revised 8 January 2007; accepted 23 January 2007.

Table 1 Clinical profile and laboratory data of the patients

Patient	Age/sex	Duration since onset	Symptoms	Cerebrospinal fluid		Anti-HTLV-I antibodies*		T2 lesion in MRI
				Cell/mm^3	Protein (mg/dl)	CSF	Serum	
1	63/F	4 mo	SP, UD	41	57	×2048	×32768	C2–T10
2	57/F	3 mo	SP, UD	46	73	×4096	×65536	C3–T3
3	75/F	6 mo	TP, UD, dementia	3	59	×16	512	C2–T6
4	54/F	4 mo	SP, UD,	10	51	×512	×16384	C3–T9
5	63/F	6 mo	SP, UD	16	46	×1024	×16384	C2–T9
6	58/M	7 mo	SP, tremor in hands, UD	82	73	×2048	×16384	C3–T9
7	54/M	7 mo	SP, UD	12	48	×64	×8192	C2
8	70/F	5 mo	SP, hypoesthesia of deep sens. in hands	1	29	×512	×8192	C1–4
9	79/F	3 mo	SP, Dys in hands,	1	35	×32	×2048	C3–5
10	72/M	6 mo	SP, UD, Dys. in hands	24	129	×512	×32768	T4–9
11	66/M	3 mo	SP, UD	3	38	×8	×2048	T1–6

TP = tetraparesis; SP = spastic paraparesis; UD = urinary disturbance; Dys = dysdiadochokinesis. *Anti-HTLV-I antibody (particle agglutinin method); sens = sensation.

fluid (CSF). These patients all had abnormal spinal MRI findings. We analyzed the immunological and virological aspects of the patients' conditions, and considered the role of HTLV-I infection in these patients.

Results

Laboratory data
The laboratory data are summarized in Table 1. In all cases, anti-HTLV-I antibodies were present in both the serum and the cerebrospinal fluid (CSF). CSF examination revealed mild pleocytosis in 8 out of 15 cases, and elevated protein levels in 11 out of 15 cases.

Spinal MRI findings
CT type: Six patients (patients 1 to 6) had CT type abnormalities seen in their spinal MRI (Figure 1A to C). High signal intensity extended from the upper cervical to the lower thoracic cord levels. Spinal cord swelling was found in three patients. No Gd enhancement was found in any of the patients. Axial imaging revealed that high signal intensity lesions were symmetrically localized in the center, bilateral lateral, or posterior columns. Among six patients, we could follow up three cases for 3 years. Follow-up MRIs revealed decreased spinal cord swelling, with the disappearance of high-intensity signals on T2WI in all patients (Figure 1D to F). Spinal cord atrophy was subsequently observed in these patients (Figure 2).

C type: Three patients (patients 7 to 9) had high-intensity lesions in cervical cord levels on T2WI (Figures 3, 4). In patients 7 and 9, high-intensity signals were localized in the lateral or posterior columns in T2WI. Patient 8, who showed severe impairment of

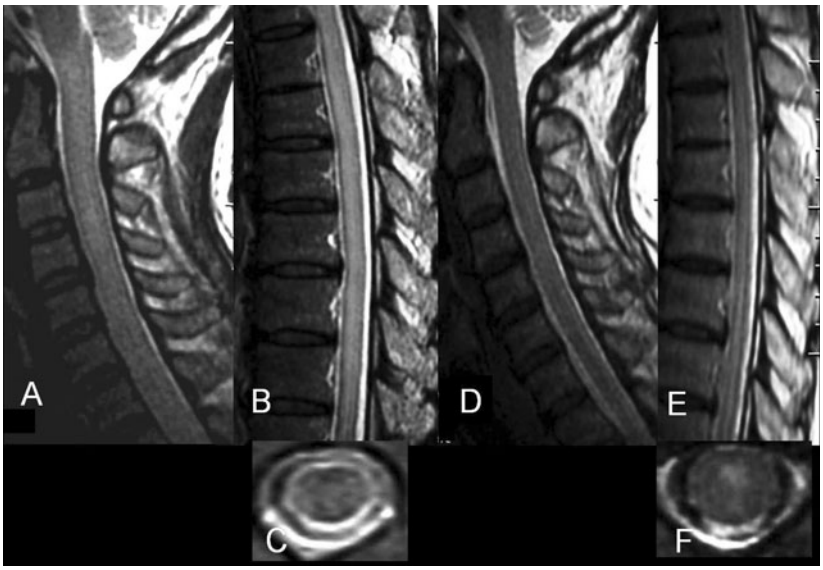

Figure 1 MRI from patient 1, before treatment (**A–C**), and after treatment (**D–F**). T2WI (sagittal: **A, B, D, E;** axial: **C, F**). Note diffuse spinal cord swelling with high intensity signals from cervical to thoracic cord levels.

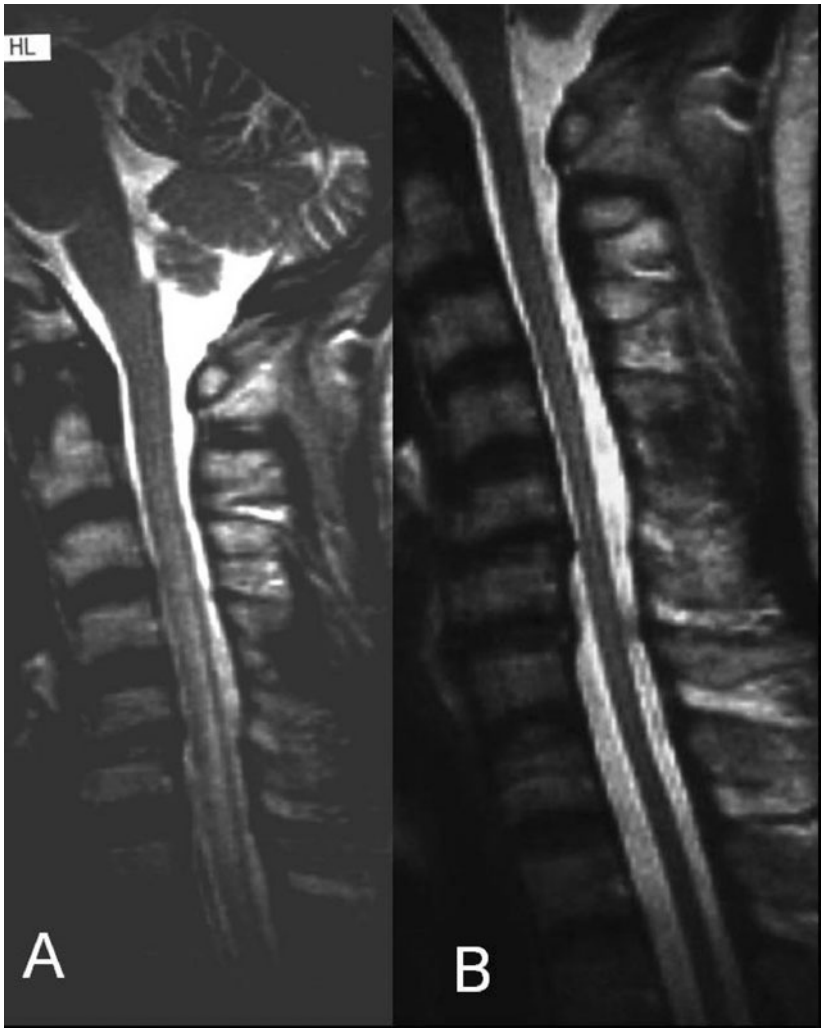

Figure 2 MRI from patient 2. Sagittal T1WI before (**A**) and after (**B**) treatment. Spinal cord swelling with high intensity signals on T2WI was reduced followed by spinal cord atrophy.

deep sensation in both upper limbs, had high-signal intensity lesions localized bilaterally in the fascicules cuneatus (Figure 3C, D). In patient 9, focal Gd enhancement was found in the lateral columns bilaterally in T1WI, and high intensity areas were found in T2WI (Figure 4). Among three patients, we could follow-up the patient 9 for 3 years. Follow-up MRI revealed the disappearance of high-intensity signal on T2WI 1 year later.

T type: Two patients (cases 10 and 11) had high-signal-intensity lesions in the thoracic cord levels on T2WI (patient 10: Figure 5A; patient 11: Figure 5E). In patient 10, high-intensity lesions were localized in the central part of the spinal cord in T2WI (Fig. 5B), and Gd-enhancing lesions were localized in the lateral columns on both sides (Fig. 5C). Both patients had paraparesis with constricting pain on the abdomen. We were able to follow patient 10 for 2 years. Follow-up MRI revealed the disappearance of high-intensity signal on T2WI 1 year later (Figure 5D).

The risk for developing HAM/TSP
Among the patients with HAM/TSP and healthy carriers (HCs), 39 cases showed odds above 3.0. In these 39 cases, 37 cases (95%) were HAM/TSP, and only 2 cases (5%) were HCs. The odds for HAM/TSP in the patients of the present study were comparable to those seen in the control cohort of patients with HAM/TSP and higher than those of the healthy carriers (Figure 6, Table 2).

Discussion

The 11 patients in this study had several features in common: (1) progressive myelopathy with duration of several months, (2) anti-HTLV-I antibodies in serum and CSF, (3) abnormal T2 lesions in the spinal cord with or without spinal cord swelling, and (4) high odds scores for developing HAM/TSP. We screened for other possible causes of myelopathy

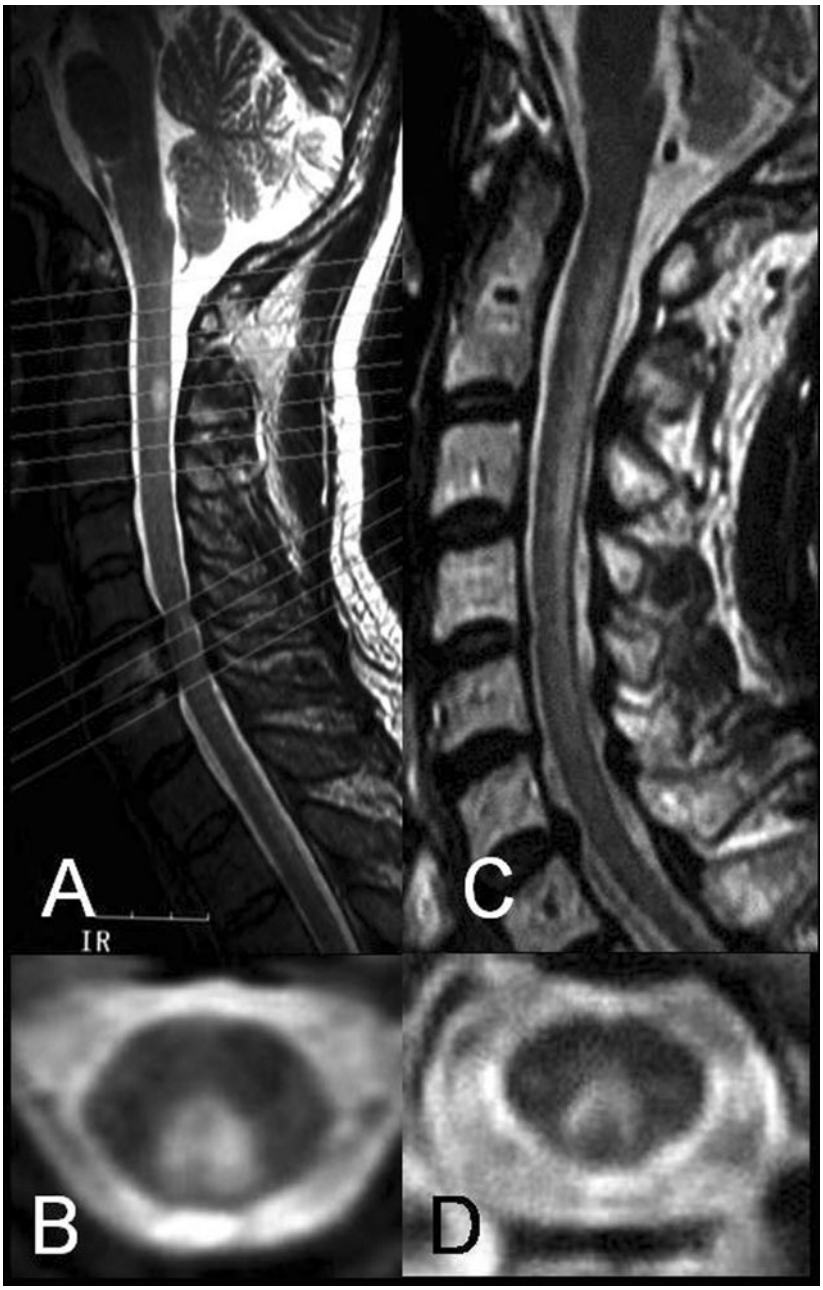

Figure 3 Spinal cord MRI from patients 7 (**A, B**) and 8 (**C, D**). Sagittal T2WI revealed high intensity lesions at C2–3 levels in patient 7 (**A**) and at C1–4 levels in patient 8 (**C**). Axial T2WI (**B, D**) revealed bilateral high intensity lesions in the posterior columns.

such as neurosarcoidosis, parasitic myelitis, multiple sclerosis, and myelitis associated with collagen-vascular disease, but these diseases were unlikely in any of the 11 cases. We then suspected that these cases might be associated with HTLV-I infection.

The most striking departure from the typical HAM/TSP clinical picture is the presence of abnormal MRI lesions in the spinal cord. This is in contrast to the typical HAM/TSP, the hallmark finding being because spinal cord atrophy predominantly involving the thoracic cord levels without gadolinium-DTPA enhancement. Abnormal MRI lesions in the present patients were classified as CT, C, and T types. In each type, there was swelling of the spinal cords with high intensity lesions in T2WI, which were located mainly in bilateral posterior columns, posterior horns, or lateral columns. Abnormalities in the CSF, including elevated protein levels or pleocytosis, are more frequent in patients with CT-type lesions, suggesting widespread inflammation in spinal cords. Recently, several cases of HAM/TSP with MRI abnormalities in the spinal cord have been reported (Shakudo *et al*, 1999; Watanabe

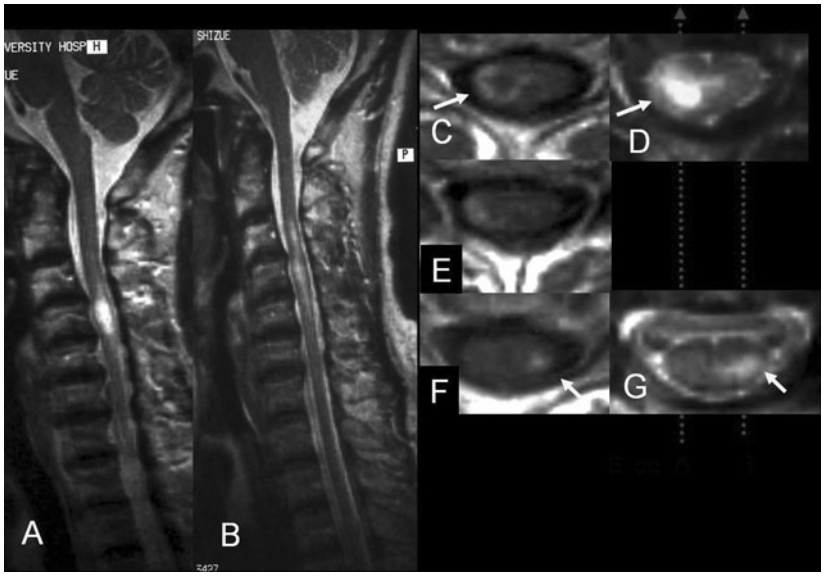

Figure 4 Spinal cord MRI of patient 9. Sagittal T2WI revealed high intensity lesions at the C3 (**A**) and C3–5 (**B**) levels. Axial T2WI (**D, G**) showed high intensity lesions in the lateral to posterior posterior columns on both sides. Focal Gd-enhancing lesions (*arrow*) were localized in the lateral columns bilaterally (**C, E**, and **F**).

et al, 2001; Tajima *et al*, 2003; Levin *et al*, 1997). These changes consisted of spinal cord swelling with high signal intensity and contrast enhancement from the cervical to the thoracic levels. In addition, we reported four patients who developed slowly progressive myelopathy with abnormal MRI lesions at the cervical cord levels (Umehara *et al*, 2004). Two patients with HAM/TSP also developed transient T2 lesions that were evident in a cervical cord MRI (Umehara *et al*, 2006). These reports suggest that MRI lesions in HAM/TSP may be more variable than previously expected. This is not surprising because neuropathological studies of HAM/TSP revealed widespread inflammation in the CNS (Aye *et al*,

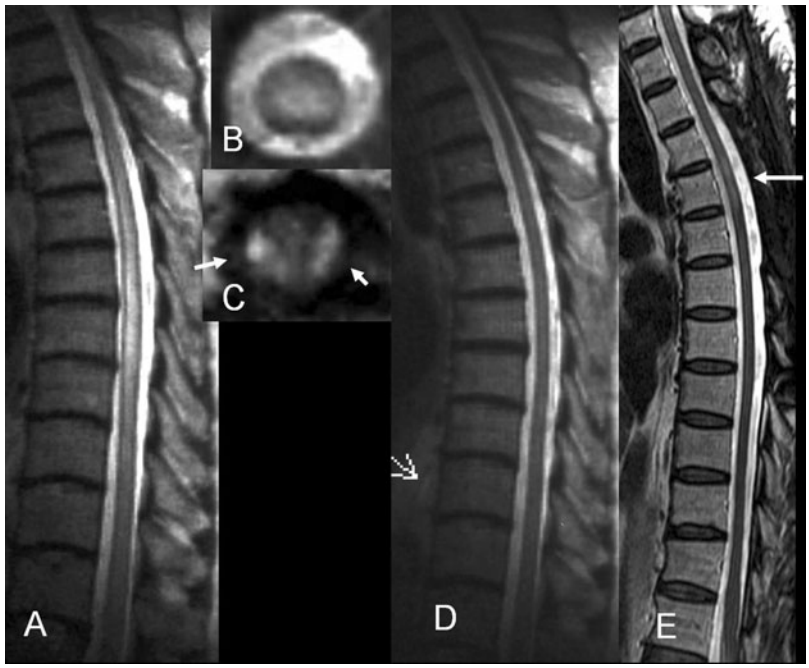

Figure 5 MRI from patients 10 and 11. Patient 10 (**A–D**): Sagittal T2WI revealed a high-intensity lesion at the middle thoracic cord levels with spinal cord swelling (**A**). Axial T2WI showed high intensity lesions at the center of spinal cord (**B**), and Gd-enhanced axial T1WI revealed focal enhancement in lateral columns on both sides (**C**). High-intensity lesions at the thoracic cord levels disappeared 1 year later (**D**). Patient 11 (**E**): Sagittal T2WI revealed a high-intensity lesion at the upper thoracic cord level (*arrow*).

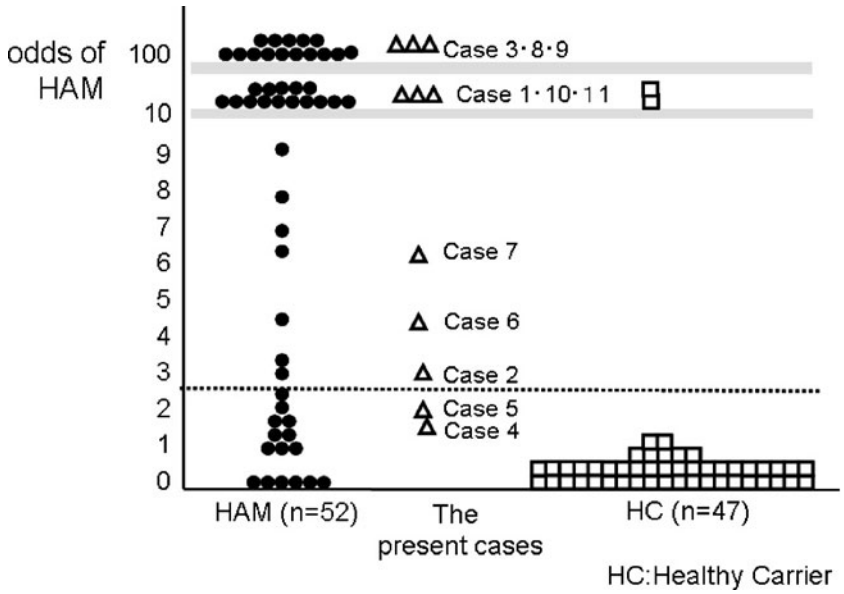

Figure 6 Odds of developing HAM/TSP. All patients (patients 1 to 11) showed high odds of developing HAM/TSP.

2000). The stage of the disease process may be important for appearance of abnormalities in the spinal MRI. All cases in the present paper were examined within 7 months after the onset of symptoms, and all cases showed rapidly progressive course. The severity of spinal cord inflammation in HAM/TSP correlates roughly with the duration of the disease process (Aye *et al*, 2000, Umehara *et al*, 1993). Perivascular accumulation of inflammatory cells and parenchymal exudation of T lymphocytes and monocytes apparently subsided approximately 3 years after onset. Thus, spinal MRIs may reflect early stages of spinal cord lesion in rapidly progressive type of HAM/TSP. In addition, activities of inflammation in the CNS of HAM/TSP are different among the lesions. Iwasaki *et al* (1992) demonstrated that active inflammatory lesions are found in the pons, although spinal cord showed burned-out changes consisted of degenerative changes without active inflammatory reactions. Thus, T2 lesions in the spinal cords in the present cases may reflect the sites of active inflammation, concomitant with inactive lesions in the other normal-looking spinal cord on MRI.

In patient 9 (C type), high-intensity lesions were located in both lateral columns with focal Gd enhancement. We observed perivascular accumulation of degenerated axons in both lateral columns in the spinal cord in HAM/TSP (Umehara *et al*, 2004). Distribution of the MRI abnormalities in each case is related to the pathology of HAM/TSP. Patient 8 had impairment of the deep sensation in upper limbs, and somatosensory evoked potential (SEP) and MRI showed involvement of the posterior columns at the cervical level.

A major risk factor for developing HAM/TSP is the provirus load. The median proviral load was approximately 16 times higher in HAM/TSP patients than in HCs, and a high proviral load is also associated with an increased risk for progression to HAM/TSP (Nagai *et al*, 1998). In the present study, all patients had higher HTLV-I proviral load than HCs. Human leukocyte antigen (HLA)-A02 and -Cw08 genes were

Table 2 Risk for developing HAM/TSP

Patient	Proviral load*	Tax subtype	HLA-Cw08	HLA-A2	TNF-α C-863A#	SDF-1 b G801A**	HAM odds
1	303	B	N	N	CC	AA	16.5
2	121	B	N	N	CC	GG	3.5
3	114	B	N	N	CC	GA	133.7
4	110	B	N	N	AC	GG	1.8
5	237	B	+	N	CC	AA	2.1
6	193	B	N	N	AC	GA	4.0
7	459	B	N	+	AC	GA	6.7
8	537	A	N	N	CC	AA	415
9	94	A	N	+	CC	GG	2247.6
10	67	B	+	N	CC	GG	39.2
11	797	B	N	N	CC	AA	51.4

*Tax copies/10^4 PBMCs. N = negative.
**SDF-1 + 801 allele (GG, GA, or AA).
#TNF-α promotor 863 allele (AA, AC, or CC).

associated with a lower HTLV-I proviral load and protection from HAM/TSP, whereas HLA-DRB1* 0101 and -DRB*5401 were associated with susceptibility to HAM/TSP. (Jeffery *et al*, 1999, 2000). Moreover, we demonstrated the presence of non-HLA genetic risk factors such as tumor necrosis factor (TNF)-α, stromal cell-derived factor-1 (SDF-1), and interleukin (IL)-15 (Vine *et al*, 2002) as well as the association between HTLV-I Tax gene variation and the risk for HAM/TSP (Furukawa *et al*, 2000). From these observations, we can identify approximately 88% of the cases of HAM/TSP in the Kagoshima cohort. We calculated the odds for developing HAM/TSP in these patients. The results are summarized in Table 1 and Figure 4. Among the patients with HAM/TSP and HCs, 39 cases showed odds above 3.0. In these 39 cases, 37 cases (95%) were HAM/TSP, and only 2 cases (5%) were HCs. In the patients in our study, the odds of developing HAM/TSP were comparable to those of the patients in the control group with HAM/TSP and they were higher than those of healthy carriers. These findings suggest that these patients have comparable immunological and virological backgrounds leading to the development of HAM/TSP.

In conclusion, HTLV-I infection in these patients is not likely to be coincidental, but may be closely associated with HAM/TSP. This report is the first comprehensive MRI study of an early stage of HAM/TSP. Spinal MRI abnormalities in these cases may reflect active inflammatory lesions in the spinal cords of HAM/TSP, especially in cases of rapidly progressive type.

Methods

The study participants were eleven Japanese patients who had the following two features: spinal MRI abnormalities and the presence of anti-HTLV-I antibodies in both serum and CSF. We conducted a clinical and immunological analysis of each case.

Neurological symptoms
Clinical features of these patients are summarized in Table 1. The patient age ranged from 54 to 79 years old (mean 64). Patient contact occurred 3 to 7 months after the onset of illness. Frequent initial symptoms were gait disturbance or numbness in the lower limbs (9 out of 11 cases). Three patients had numbness or a lack of coordination in the upper limbs. Neurological examination on admission revealed paraparesis in all cases. Three patients had dysdiadochokinesis in both hands. Two patients experienced disturbances of deep sensation in hands. Nine patients had bladder dysfunction.

MRI findings
Based on T2WI, spinal MRI abnormalities were classified into three categories: (1) cervical to thoracic (CT) type (high signal intensity on T2WI extending from the cervical to thoracic cord levels with or without gadolinium [Gd] enhancement); (2) cervical (C) type (high signal intensity on T2WI localized in the cervical cord level with or without Gd enhancement); and (3) thoracic (T) type (high signal intensity on T2WI localized in the thoracic cord level with or without Gd enhancement).

Evaluation of the risk of HAM/TSP
We calculated the odds that an HTLV-I–infected individual living in the Kagoshima prefecture, of a specified genotype, age, and proviral load, has HAM/TSP by an equation specifically developed for this population (Vine *et al*, 2002; Nose *et al*, 2006). Blood samples from patients 1 to 3 were analyzed upon obtaining informed consent. For the controls, we used a study cohort that consisted of 52 patients with HAM/TSP receiving care at the Department of Neurology and Geriatrics, Kagoshima University (Kagoshima, Japan) and 47 healthy carriers (HCs) of HTLV-I randomly selected from the same geographical location, as described elsewhere (Jeffery *et al*, 1999, 2000). All individuals screened were of Japanese descent and resided within the Kagoshima prefecture in Kyushu, Japan. The diagnosis of HAM/TSP was made in accordance with World Health Organization criteria (Osame, 1990). Peripheral blood was obtained from all individuals upon obtaining informed consent. Fresh peripheral blood mononuclear cells (PBMCs) were obtained by density gradient centrifugation using a Histopaque-1077 instrument (Sigma, Tokyo, Japan) and washed three times with phosphate-buffered saline (PBS) containing 1% fetal calf serum (FCS). Isolated pumps were cryopreserved in liquid nitrogen until use. Genomic DNA was extracted from PBMCs using a QIAamp blood kit (Qiagen Ltd, Tokyo, Japan) according to the manufacturer's instructions.

Genotyping methods for non-HLA candidate genes: For each candidate gene, we went on to do genotyping either by DNA sequencing or by polymerase chain reaction (PCR) with allele-specific primers as previously described (Jeffery *et al*, 1999).

HLA typing: The results of the molecular genotyping of class I and class II HLA loci in this cohort have been reported elsewhere (Jeffery *et al*, 1999).

HTLV-I genotyping: Two subgroups (A and B) of the cosmopolitan genotype of HTLV-I are present in Kagoshima, Japan. The molecular typing of the HTLV-I *tax* gene was done (as described elsewhere) to identify the HTLV-I subgroup present in each infected subject (Furukawa *et al*, 2000).

Proviral load measurement: The proviral load in PBMCs was measured using real-time PCR with an ABI 7700 sequence detection system (Applied Biosystems). Using β-actin as an internal control, the amount of HTLV-1 proviral DNA was calculated by

the following formula: copy number of HTLV-1 (pX) per 1×10^4 PBMCs = (copy number of pX/(copy number of β-actin/2)) $\times 10^4$. All samples were amplified and analyzed in triplicate, as described elsewhere (Jeffery *et al*, 1999).

The odds of developing HAM/TSP: We calculated the odds that an HTLV-I–infected individual of a specific genotype, age, and provirus load has HAM/TSP by using the equation based on the logistic regression analysis in the Kagoshima cohort as previously described (Vine *et al*, 2002). A worked example is as follows: an HTLV-I–infected individual in Kagoshima, 60 years old, with a log10 (proviral load) of 2.5 with the genotype *TNF* $-863A^+$, *SDF-1* + *801AA*, *HLA-A*02*$^-$, *HLA-Cw*08*$^+$, HTLV-I subgroup B has a predicted ln odds of HAM/TSP of $-1.716 - (0.145 \times 60) + (0.003 \times 60^2) + (0.46 \times 2.5) + (0.487 \times 2.5^2) + 3.057 - (4.616 \times 2.5) + (1.476 \times 2.5^2) - 1.689 - 0.894 - 1.587 = 1.14975$. That is, this HTLV-1–infected individual's odds of developing HAM/TSP = $\exp(1.14975) = 3.157403$.

References

Aye MM, Matsuoka E, Moritoyo T, Umehara F, Suehara M, Hokezu Y, Yamanaka H, Isashiki Y, Osame M, Izumo S (2000). Histopathological analysis of four autopsy cases of HTLV-I-associated myelopathy/tropical spastic paraparesis: inflammatory changes occur simultaneously in the entire central nervous system. *Acta Neuropathol (Berl)* **100:** 245–252.

Furukawa Y, Yamashita M, Usuku K, Izumo S, Nakagawa M, Osame M (2000). Phylogenetic subgroups of human T cell lymphotropic virus (HTLV) type I in the tax gene and their association with different risks for HTLV-I-associated myelopathy/tropical spastic paraparesis. *J Infect Dis* **182:** 1343–1349.

Gessain A, Barin F, Vernant JC, Gout O, Maurs L, Calender A, de The G (1985). Antibodies to human T-lymphotropic virus type-I in patients with tropical spastic paraparesis. *Lancet* **2:** 407–410.

Iwasaki Y (1990). Pathology of chronic myelopathy associated with HTLV-I infection (HAM/TSP). *J Neurol Sci* **96:** 103–123.

Iwasaki Y, Ohara Y, Kobayashi I, Akizuki S (1992). Infiltration of helper/inducer T lymphocytes heralds central nervous system damage in human T-cell leukemia virus infection. *Am J Pathol* **140:** 1003–1008.

Jeffery KJ, Siddiqui AA, Bunce M, Lloyd AL, Vine AM, Witkover AD, Izumo S, Usuku K, Welsh KI, Osame M, Bangham CR (2000). The influence of HLA class I alleles and heterozygosity on the outcome of human T cell lymphotropic virus type I infection. *J Immunol* **165:** 7278–7284.

Jeffery KJ, Usuku K, Hall SE, Matsumoto W, Taylor GP, Procter J, Bunce M, Ogg GS, Welsh KI, Weber JN, Lloyd AL, Nowak MA, Nagai M, Kodama D, Izumo S, Osame M, Bangham CR (1999). HLA alleles determine human T-lymphotropic virus-I (HTLV-I) proviral load and the risk of HTLV-I-associated myelopathy. *Proc Natl Acad Sci U S A* **96:** 3848–3853.

Levin MC, Lehky TJ, Flerlage AN, Katz D, Kingma DW, Jaffe ES, Heiss JD, Patronas N, McFarland HF, Jacobson S (1997). Immunologic analysis of a spinal cord-biopsy specimen from a patient with human T-cell lymphotropic virus type I-associated neurologic disease. *New Engl J Med* **336:** 839–844.

Nagai M, Usuku K, Matsumoto W, Kodama D, Takenouchi N, Moritoyo T, Hashiguchi S, Ichinose M, Bangham CR, Izumo S, Osame M (1998). Analysis of HTLV-I proviral load in 202 HAM/TSP patients and 243 asymptomatic HTLV-I carriers: high proviral load strongly predisposes to HAM/TSP. *J NeuroVirol* **4:** 586–593.

Nose H, Saito M, Usuku K, Sabouri AH, Matsuzaki T, Kubota R, Eiraku N, Furukawa Y, Izumo S, Arimura K, Osame M (2006). Clinical symptoms and the odds of human T-cell lymphotropic virus type 1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) in healthy virus carriers: application of best-fit logistic regression equation based on host genotype, age and provirus load. *J NeuroVirol* **12:** 171–177.

Osame M (1990). Review of WHO Kagoshima meeting and diagnostic guidelines for HAM/TSP. In: *Human Retrovirology: HTLV*. Blattner WA (ed). New York: Raven Press, pp 191–197.

Osame M, Usuku K, Izumo S, Ijichi N, Amitani H, Igata A, Matsumoto M, Tara M (1986). HTLV-I associated myelopathy, a new clinical entity. *Lancet* **1:** 1031–1032.

Umehara F, Osame M (2003). Histological analysis of HAM/TSP pathogenesis. In: *Two decades of adult T-cell leukemia and HTLV-I research*. Sugamura K, Uchiyama T, Masao M, Kannagi M (eds). Tokyo: Japan Scientific Societies Press, pp 141–148.

Shakudo M, Inoue Y, Tukada T (1999). HTLV-I-associated myelopathy: acute progression and atypical MR findings. *Am J Neuroradiol* **20:** 1417–1421.

Tajima Y, Kishimoto R, Sudoh K, Miyazaki Y, Kikuchi S, Tashiro K (2003). Spinal magnetic resonance image alterations in human T-lymphotropic virus type I-associated myelopathy patients before and after immunomodulating treatment. *J Neurol* **250:** 750–753.

Umehara F, Izumo S, Nakagawa M, Ronquillo AT, Takahashi K, Matsumuro K, Sato E, Osame M (1993). Immunocytochemical analysis of the cellular infiltrate in the spinal cord lesions in HTLV-I associated myelopathy. *J Neuropathol Exp Neurol* **52:** 424–430.

Umehara F, Nagatomo S, Yoshishige K, Saito M, Furukawa Y, Usuku K, Osame M (2004). Chronic progressive cervical myelopathy with HTLV-I infection: variant form of HAM/TSP? *Neurology* **63:** 1276–1280.

Umehara F, Tokunaga N, Hokezu Y, Hokonohara E, Yoshishige K, Shiraishi T, Okubo R, Osame M (2006). Relapsing cervical cord lesions on MRI in patients with HTLV-I-associated myelopathy.*Neurology* **66:** 289.

Vine AM, Witkover AD, Lloyd AL, Jeffery KJ, Siddiqui A, Marshall SE, Bunce M, Eiraku N, Izumo S, Usuku K, Osame M, Bangham CR (2002). Polygenic control of human T lymphotropic virus type I (HTLV-I) provirus load and the risk of HTLV-I-associated myelopathy/tropical spastic paraparesis. *J Infect Dis* **186:** 932–939.

Watanabe M, Yamashita T, Hara A, Murakami T, Ando Y, Uyama E, Mita S, Uchino M (2001). High signal intensity in the spinal cord on T2-weighted images in rapidly progressive tropical spastic paresis. *Neuroradiology* **43:** 231–233.