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Conventional magnetic resonance imaging features in patients with tropical spastic paraparesis

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Conventional brain and spinal cord magnetic resonance images were performed in 21 patients with human T-cell lymphotropic virus (HTLV)-1 associated myelopathy/tropical spastic paraparesis, to assess the role of conventional magnetic resonance imaging (MRI) in the disease diagnosis. These patients had no other central nervous system conditions or related risk factors at the time of tropical spastic paraparesis diagnosis. Eleven (52.4%) patients showed nonspecific brain abnormalities on T2-weighted images. The majority (77.2%) of brain abnormalities were located in the deep white matter. A transient contrast-enhancing lesion was identified in the brain of only one patient. In the brain of another patient, 9.0% of the T2-hyperintense lesion load was hypointense on the correspondent T1-weighted images. No differences in terms of demographic, biological, or clinical variables were present between patients with abnormal brain images and those with normal brain magnetic resonance images. Spinal cord T2-weighted images were abnormal in three (14.3%) patients. In one of these three patients, a diffuse but transient edema was found along the entire tract of the spinal cord. White matter lesions were present in the central nervous system of 60% of the cases in this study. However, no correlations between magnetic resonance imaging and clinical findings, and no specificity of lesions were observed. Hence, conventional magnetic resonance imaging is a sensitive but not highly specific tool for diagnosis of tropical spastic paraparesis. *Journal of NeuroVirology* (2005) **11,** 525–534.

Keywords: brain; disability; HTLV-1; magnetic resonance imaging; spinal cord; tropical spastic paraparesis

Introduction

Human T-cell lymphotropic virus type I (HTLV-I) is a type C retrovirus infecting 10 to 20 million people worldwide (Geissan and Gout, 1992). The virus persists latently in the majority of carriers, but may cause a wide spectrum of diseases in other individuals. Almost 3% of infected people develop a progressive neurological disorder known as HTLV-I–associated myelopathy/tropical spastic paraparesis (HAM/TSP) (Jacobson, 2002). The neuropathogenesis of the disease is not well understood, and may vary among patients or within a patient over time. The virus persistently infects CD4+ T lymphocytes (Kubota *et al*, 1994; Moritoyo *et al*, 1996) causing a strong immune response in the central nervous system (CNS). Such a reaction involves CD8+ cytotoxic T cells (Jacobson *et al*, 1990), B cells (Furukawa *et al*, 2000), and macrophages to a lesser extent (Umehara *et al*, 1994), resulting in cellular inflammation and destruction. Humoral autoimmune mechanisms have been implicated in the pathogenesis of the disease as well (Jernigan *et al*, 2003; Levin and Jacobson, 1997).

The spinal cord is most severely affected primarily at the thoracic level, and major neurological manifestations of HAM/TSP include spinal cord-related symptoms and signs (Osame, 1990; Nakagawa *et al*,

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1995). Nonetheless, HTLV-I is known to cause disease in the brain as well. Cerebellar and cranial impairments (Osame, 1990; Nakagawa *et al*, 1995; Roman and Roman, 1988) as well as seizures (Smith *et al*, 1992) have been observed in patients with HAM/TSP. Subtle brain involvement is also indicated by auditory, visual, and sensory event–related potentials as well as electroencephalographic abnormalities (Smith *et al*, 1992; Fukushima *et al*, 1994; Kira *et al*, 1988; Cruickshank *et al*, 1989). Brain lesions have been described in postmortem studies of some HAM/TSP cases (Cartier *et al*, 1997; Ogata *et al*, 1993). The pathology of such brain lesions closely correlates with features of spinal cord lesions (Aye *et al*, 2000).

At the present time, the diagnosis of HAM/TSP is based upon clinical (i.e., rating disability) and biological (i.e., blood proviral load) findings. There is still considerable uncertainty about MRI findings of patients with HAM/TSP, and there is no clear evidence as to whether conventional MRI plays a relevant role in diagnosing and monitoring HAM/TSP in daily clinical practice. To provide more insight into this issue, we describe conventional CNS magnetic resonance imaging (MRI) characteristics in our cohort of patients with HAM/TSP. Specifically, we define whether additional useful information can be derived from conventional MRI in patients with HAM/TSP at the time of their initial visit to a neurology center.

Results

Clinical and MRI findings of the patients

Table 1 summarizes the demographic, biological, and clinical characteristics of the patients. Associated autoimmune diseases were found in a total of nine (42.9%) patients, of which three had more than one concomitant autoimmune disease. Four patients had uveitis, three patients had thyroiditis, one patient had polymiositis, and one patient had lymphocytic alveolitis. There were no associations between Expanded Disability Status Score (EDSS) score, disease duration, and viral load. Three patients were found to have keratoconjunctivitis sicca (KTS). Patients with KTS were included in the statistical analyses of this paper, but their MRI characteristics are described separately. Ten (47.6%) patients had normal brain MRIs, and 11 (52.4%) patients had abnormal brain MRIs characterized by nonspecific T2 lesions. There were no differences in terms of demographic, biological, or clinical variables between these two groups of patients. Three patients (14.3%) were found to show abnormalities on spinal cord T2-weighted images.

Table 2 Summary of demographic and clinical characteristics of the patients

Patients number	21
Gender	13 females/8 males
Age (years)*	48.0 (± 13.1)
Ethnicity	15 African-American**, 4 Caucasians, 2 Hispanic
Disease duration (years)*	8.2 (±5.3)
EDSS*	5.8 (±1.8)
Clinical brain signs***	15 (71.4)
Clinical spinal cord signs***	21 (100.0)
Proviral load*#	25.0 (±19.9)
Associated autoimmune diseases***	9 (42.9)

*Mean (± standard deviation).
**Includes 1 patient born in Western Africa and 7 patients born in the Caribbean.
***Number of patients (percentage).
#Copy number of HTLV-1 per 100 cells.

Characterization of brain lesions in patients with abnormal MRIs

Table 2 shows the number and median size of lesions on FLAIR/T2-weighted brain images for each of the eight HAM/TSP individuals without KTS. Three patients were found to have dirty white matter (WM) along the course of the cortical-spinal tract (patients 1 to 3 in Table 2). In patient 3, the

Table 1 Features on abnormal fluid attenuated inversion recovery/T2-weighted MRIs in patients without keratoconjunctivitis sicca

			Brain lesions					
				Number of lesions				
Pt	*EDSS*	*Cord lesions*	*Size (mm^3) (median)*	*Total*	*PF*	*PV*	*JC*	*D*
1*	6.5	+		—				
2*	7.0	−		—				
3*	6.5	−	70.3	11		4	2	5
4	6.0	−	44.8	5			2	3
5	6.0	−	23.7	6				6
6	6.0	−	44.8	23		4		19
7	7.5	−	61.5	31	1		6	24
8	6.5	+	105.5	51	6	4		41
				127	7 (5.5%)	12 (9.4%)	10 (7.9%)	98 (77.2%)

*Patients with dirty white matter; Pt = patient; EDSS = Expanded Disability Status Scale score; PF = posterior fossa; PV = periventricular; JC = juxtacortical; D = discrete.

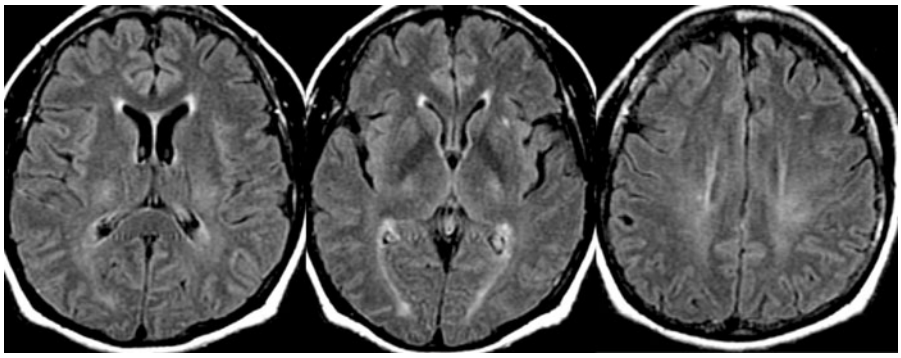

Figure 1 T2-hyperintense lesions in a patient with dirty white matter (patient 3 in Table 2) are demonstrated in these axial fluid attenuated inversion recovery images.

diffuse dirty WM was accompanied by 11 T2 lesions (Figure 1).

Two other patients exhibited ≤10 isolated WM lesions (patients 4 and 5). Three patients exhibited >10 T2 lesions (patients 6 to 8). As an example, Figure 2 shows the MRI of patient 7, who had 31 isolated T2 lesions. Patients 6 and 8 presented with diffuse and confluent hyperintense lesions distributed in the context of the deep WM, around the ventricle, at the junction between the gray matter and WM, and in the posterior fossa (PF). Figure 3a and b show examples of lesions in the PF of patient 8. A conspicuous number of black holes (BHs) was also present in the T1-weighted image of patient 8 (Figure 3c). The volume of T1 postcontrast hypointense lesions (i.e., BHs) corresponded to approximately 9% of the total lesion volume on T2-weighted images.

Table 3 summarizes the MRI findings of the three patients (patients 9 to 11) with HAM/TSP and KTS. Figure 4 shows a representative slice of the MRI of patient 11 (see Table 3), as an example. Of the three T2 abnormalities in patient 9, one enhanced. This contrast-enhancing lesion (CEL) was not present 6 months later.

Characterization of spinal cord MRI lesions

Of three individuals showing focal or diffuse T2 abnormalities in the spinal cord, two had abnormal brain MRI as well.

One patient (patient 1 in Table 2) had diffuse hyperintensities along the entire course of the spinal cord

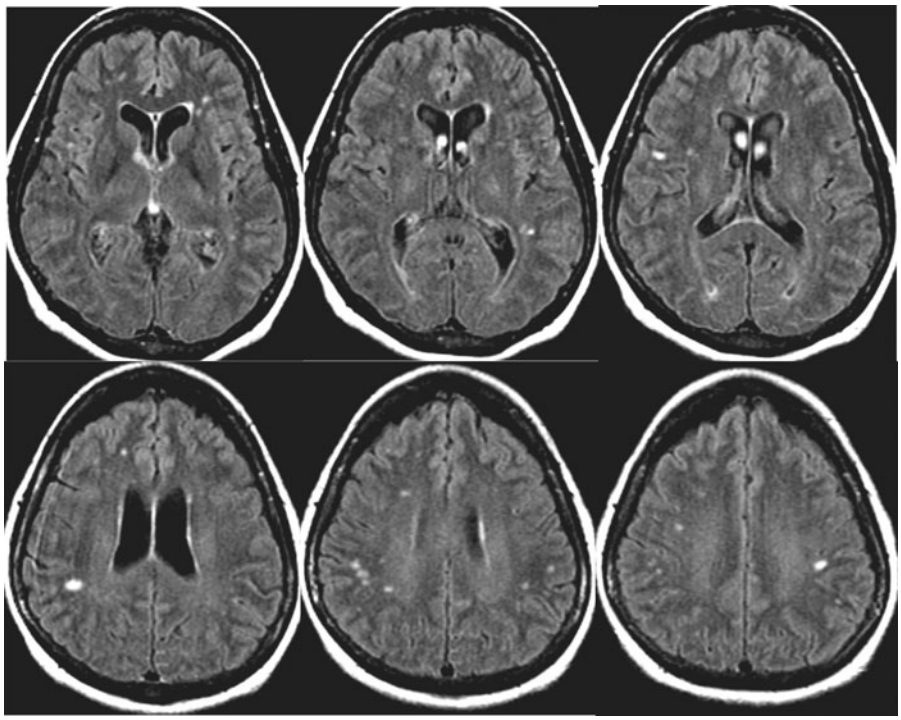

Figure 2 Some of the 31 isolated T2-hyperintense lesions are demonstrated in these axial fluid attenuated inversion recovery images of patient 7 (see Table 2).

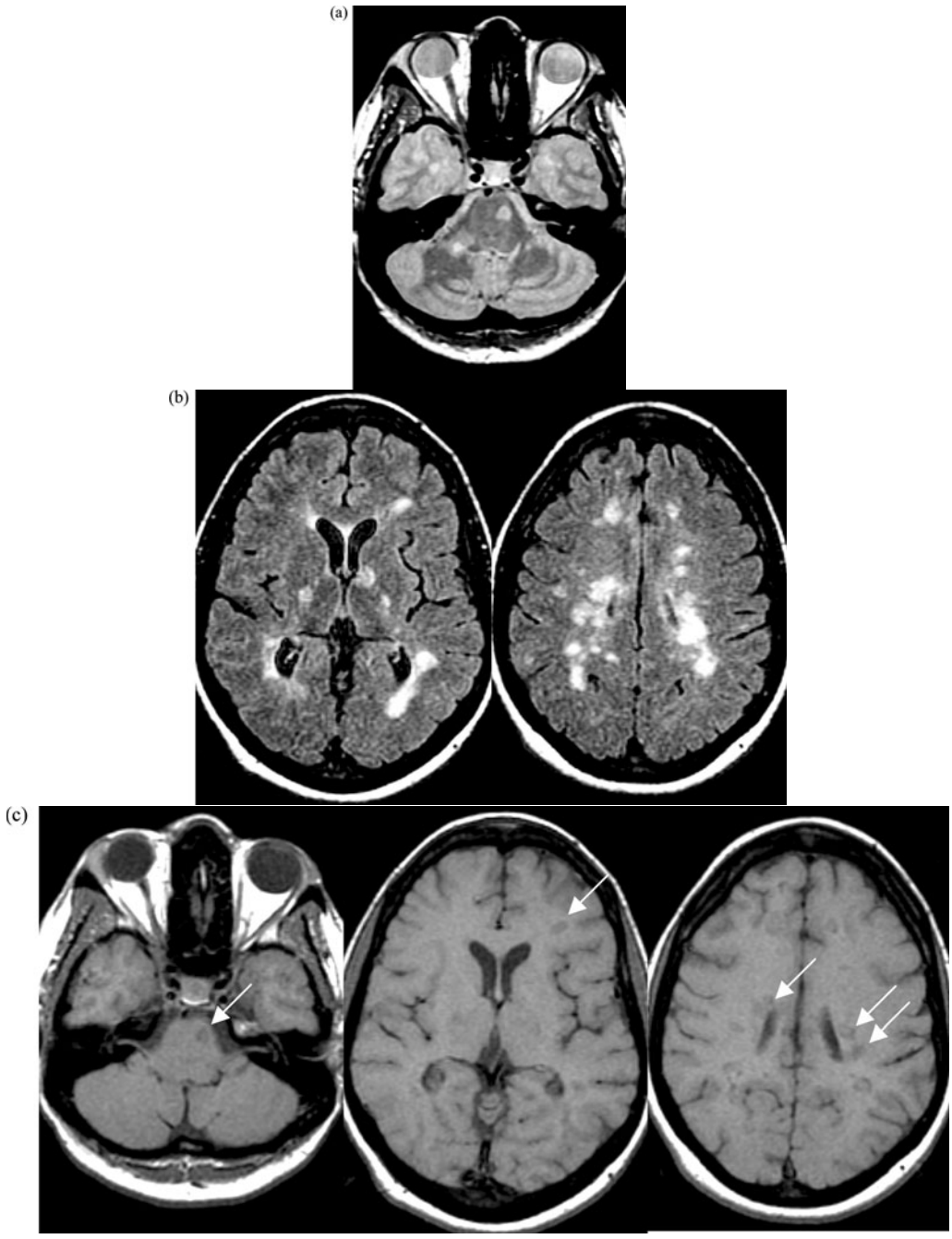

Figure 3 T2-hyperintense confluent lesions demonstrated in an axial T2W image (**a**) and fluid attenuated inversion recovery images (**b**) of patient 8 in Table 2. T1 black holes (BHs) within the white matter of the whole brain (including the posterior fossa) were also identified (**c**). The arrows highlight some of these BHs.

(Figure 5a). These hyperintense lesions were accompanied by a diffuse spinal cord edema that partially resolved 4 months later (Figure 5b). Lesions were localized at the cervical (C) levels in the other two patients: C3, C4–C5, and C6 in patient 8 (Figure 6) and C4–C6 in a second patient. (This latter patient has no assigned identification number because no corresponding MRI data is shown in the tables and figures.) The EDSS score (years of HAM and proviral loads) of the patients were 6.5 (11 years of HAM/TSP and 10.38 copy number of HTLV-1 per 100 cells), 6.5 (8 years of HAM and 2.78 copy number of HTLV-1 per 100 cells), and 8.0 (10 years of multiple sclerosis [MS] and 23.04 copy number of HTLV-1 per 100 cells), respectively. None of those patients were affected by any other immunological disorders. As stated above, patients 1 and 8 (see Table 2) had abnormal brain MRIs as well. The brain figures showed

Table 3 Features on abnormal fluid attenuated inversion recovery/T2-weighted MRIs in patients with keratoconjunctivitis sicca

			Brain lesions					
				Number of lesions				
Pt	*EDSS*	*Cord lesions*	*Size (mm^3) (median)*	*Total*	*PF*	*PV*	*JC*	*D*
9	2.5	–	70.3	3			1	2
10	4.0	–	61.5	10		2	2	6
11	8.0	–	26.3	88		5	10	73
				101	0	7 (6.9%)	13 (12.9%)	81 (80.2%)

Pt = patient; EDSS = Expanded Disability Status Scale score; PF = posterior fossa; PV = periventricular; JC = juxtacortical; D = discrete.

dirty WM in patient 1 (see Table 2; for spinal cord MRI, see Figure 5; brain MRI not shown) and confluent T2-hyperintese lesions in patient 8 (see Table 3; see Figure 6 for spinal cord MRI; see Figure 3 for brain MRI). The brain image of the third patient was found to show a small lesion within the corona radiata (i.e., lacuna), a nonspecific finding within normal limits of age. Therefore, this patient was excluded from the analysis of the brain images. None of the patients with both HAM/TSP and KTS showed abnormalities on our conventional spinal cord MRIs.

Given the small number of patients with spinal cord abnormalities, no systematic comparisons between patients with and without spinal cord lesions could be obtained.

Discussion

The aim of the present study was to characterize the brain and spinal cord MRI patterns in our cohort of patients with HAM/TSP to provide useful information for clinicians at the time of HAM/TSP diagnosis. Almost 50% of the patients were found to show some T2 abnormalities within the brain. The findings reported in these 11 patients were highly variable in

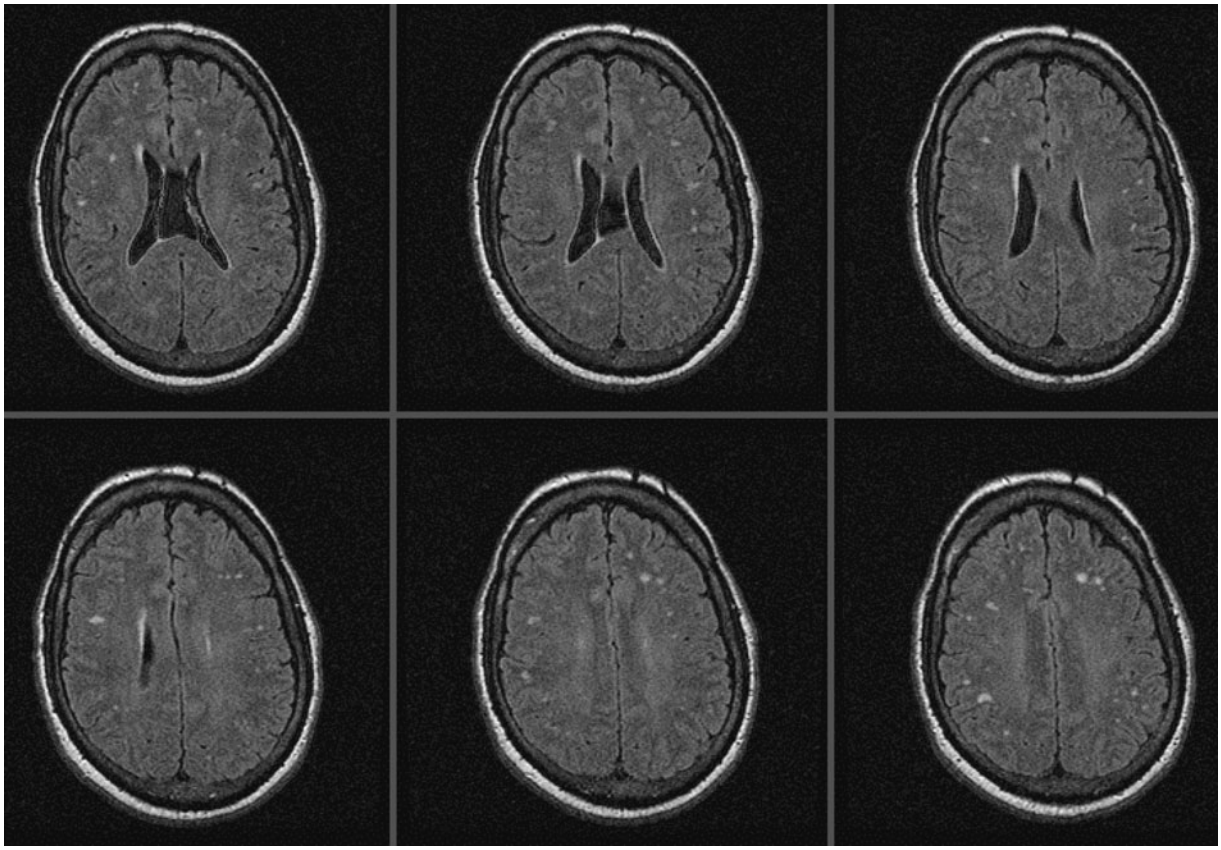

Figure 4 T2-hyperintense lesions are shown on an axial fluid attenuated inversion recovery image of patient 11 (see Table 3), who exhibited 88 countable lesions.

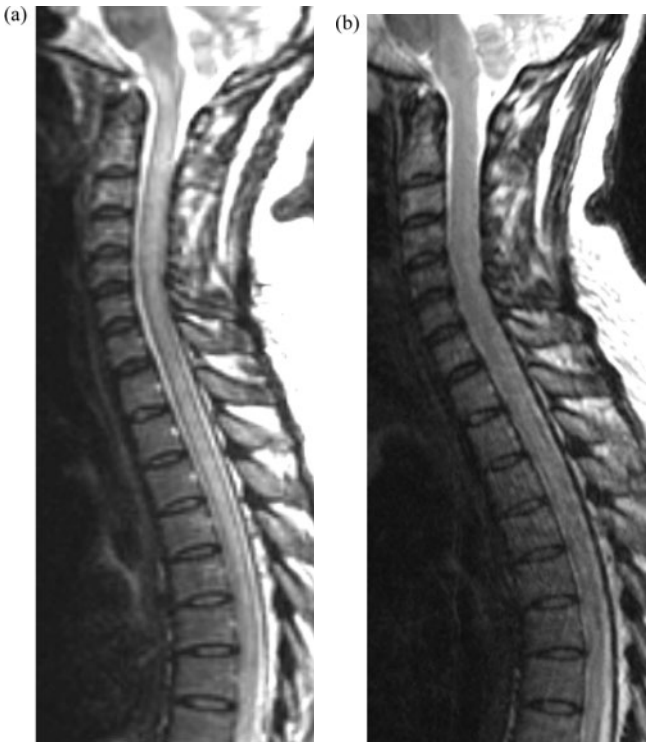

Figure 5 Spinal cord T2-hyperintense lesions and edema in a patient with diffuse abnormalities along the entire course of the spinal cord are shown in a sagital T2 image (**a**). The edema was less visible, but still present on the spinal cord MRI performed 4 months later (**b**). The brain MRI of this patient (patient 1 in Table 2) presented with dirty white matter (not shown).

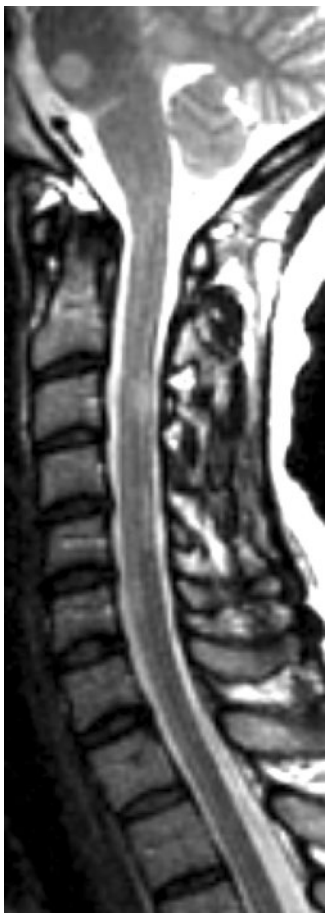

Figure 6 T2 abnormalities were localized at C3, C4–C5, and C6 in the sagital image shown here. This figure refers to patient 8 in Table 2. The brain MRI of this individual is shown in Figure 3.

terms of lesion numbers and sizes, and no defining imaging characteristics were found.

As for the incidence of T2 abnormalities in patients with HAM/TSP, high interstudy variability among previous reports has been noted, and positive brain MRIs have been found in 47% (Melo *et al*, 1993) to 100% (Howard *et al*, 2003) of the patients. It is highly likely that the lack of uniform or standardized criteria used by different authors for identifying and defining T2 abnormalities may account for such discrepancies among studies.

Presence of brain T2 abnormalities was not associated with distinct clinical and demographic patterns in patients of the present study, suggesting that an abnormal brain MRI cannot be considered as a distinctive marker for a more aggressive disease. These results are in accordance with some previous reports (Melo *et al*, 1993; Rudge *et al*, 1991; Godoy *et al*, 1995; Milagres *et al*, 2002), but do not parallel other studies that found longer disease duration and greater disability in HAM/TSP patients who had positive (i.e., at least two lesions on T2-weighted images) brain MRIs (Kira *et al*, 1988; 1991). The similarly small number of patients included in our and these latter studies may provide explanations for such interstudies differences.

In accordance with most previous findings, all the lesions were confined to the WM; no basal ganglia or gray matter lesions were seen. Almost 80% of the lesions were discrete (D), but, unlike in multiple sclerosis, few (i.e., less than 20%) were located either periventricular (PV) or juxtacorticol (JC), and a very few (i.e., about 5%) were identified in the PF. Such a pattern was observed both when considering the patients individually or as a group. As for the sites of T2 lesions in HAM/TSP patients, discordant findings have been reported. JC lesions have been rarely observed by previous authors (Kira *et al*, 1991; Godoy *et al*, 1995; Kuroda *et al*, 1995; Milagres *et al*, 2002; Howard *et al*, 2003), apart from one study in which up to 59% of the lesions observed in the HAM/TSP patient cohort were JC lesions (Kira *et al*, 1988). Very few PF lesions have been identified in previous reports (Godoy *et al*, 1995; Rudge *et al*, 1991; Milagres *et al*, 2002; Howard *et al*, 2003), as shown in our study. Moreover, infratentorial lesions have been found to be absent (Melo *et al*, 1993) or rarer in HAM/TSP patients as compared to patients with multiple sclerosis (Godoy *et al*, 1995; Rudge *et al*, 1991; Milagres *et al*, 2002; Howard *et al*, 2003) or

with other collagen-vasculitis diseases (Kuroda *et al*, 1995). PV lesions in HAM/TSP patients have been reported to be rarer than in patients with multiple sclerosis (Godoy *et al*, 1995; Rudge *et al*, 1991; Milagres *et al*, 2002; Howard *et al*, 2003), but equal in proportion (Kira *et al*, 1991) or even more common than in patients with noninflammatory neurological disorders (Kuroda *et al*, 1995). However, a recent study reported that PV halos were more common in HAM/TSP patients rather than in individuals with multiple sclerosis (Howard *et al*, 2003). Therefore, paucity of PF lesions, but not of PV and JC lesions, may potentially differentiate conventional MRI of patients with HAM/TSP as compared to patients with multiple sclerosis or other inflammatory disorders of the CNS.

A few other pathological brain abnormalities were observed besides the presence of T2-hyperintense lesions. One patient exhibited an isolated CEL that was no longer enhancing 6 months later, whereas another individual showed a high number of T1-hypointense lesions. These findings point out the role of either inflammation, as evidenced by the occurrence of CELs (Levin *et al*, 1997), or axonal loss, as displayed by the presence of T1 BHs (Bruck *et al*, 1997). Moreover, these sporadic observations show heterogeneity in the pathological process responsible for the formation of the damage in the brains of HAM/TSP patients.

The characterization of the disease in the spinal cord level was another aim of our study. We found T2 abnormalities at the cervical spinal cord level in three (11%) individuals. This is not surprising because volume loss or atrophy of the cord rather than focal lesions are known to occur more frequently in patients with HAM/TSP, motivating a further on-going study measuring the brain and spinal cord volume of this patients' cohort.

However, we still believe that this might not entirely explain the paucity of spinal cord lesions observed in our and previous cohorts of patients with HAM/TSP. Previous reports on necropsy cases of HAM/TSP suggest that inflammation of the spinal cord, especially at the thoracic level, may be a further neuropathological change occurring in HAM/TSP. However, we did not identify any patient with active inflammatory lesions (i.e., CELs) in the spinal cord and we were able to demonstrate the occurrence of fluctuating edema in one patient. As in our study, enhancement (Levin *et al*, 1997; Yanagihara *et al*, 2000; Milagres *et al*, 2002; Taujima *et al*, 2003) and diffuse edema (Taujima *et al*, 2003; Kasahata *et al*, 1999; Shakudo *et al*, 1999; Watanabe *et al*, 2001) along the entire spinal cord have been only sporadically described. T2-weighted images of the spinal cord have been found to be abnormal in about 60% of patients in previous studies (Kermode *et al*, 1990; Howard *et al*, 2003). However, other authors identified a normal signal return in the cervical spinal cord of all examined patients with HAM/TSP (Cruickshank *et al*, 1989; Rudge *et al*, 1991). Thus, there are again differences between our results and those previously reported, as well as among different studies, which can be explained in several ways. First, differences in terms of sample sizes may be a factor. Second, given the variable course of the disease within a patient, the time at which patients were imaged may contribute to such interstudies variability as well. Third, initial clinical studies have been performed on clinical 0.5-T MR units (Kira *et al*, 1991; Rudge *et al*, 1991), which may less accurately estimate lesions than MR units at higher magnetic fields (1.5-T). Finally, detection of cord lesions may be compromised by technical difficulties inherent to spinal MRI such as cord geometry, cardiac and spinal fluid pulsations, and patient cooperation (Hickman and Miller, 2000).

A possible limit of our study is the absence of populations of healthy subjects or patients with other CNS disease serving as case controls. Therefore, questions remain on the specificity of T2-weight image MRI in differentiating HAM/TSP from certain other CNS conditions such as vascular disease or related risk factors. However, because we mainly aimed at determining the role of MRI as an additional sensitive, rather than specific, paraclinical tool for the diagnosis of HAM/TSP, we believe that the present study by also confirming previous reports in the literature can still provide useful information for clinicians in the daily clinical setting. Specifically, conventional MRI may add nonspecific information to the diagnostic process of HAM/TSP, merely ruling out the possibility of the existence of other pathologies.

Materials and methods

Patients and study design

This cross-sectional study was performed at the National Institutes of Health (NIH). The National Institute of Neurological Disorders and Stroke (NINDS) institutional review board approved the study, and informed written consent was obtained from all patients. Twenty-one patients with HAM/TSP (Osame, 1990) and no other diseases of the CNS or related risk factors were consecutively enrolled. Disability was rated in each patient by means of the Expanded Disability Status Scale (EDSS) (Kurtzke, 1993) score. HTLV-I proviral DNA load in the peripheral blood mononuclear cells (PBMCs) was measured using an ABI PRISM 7700 Sequence Detector (Applied Biosystems, Foster City, CA) as previously described. (Nagai *et al*, 2001).

MRI acquisition

Each patient had brain and spinal cord MRIs concomitantly with clinical and biological evaluations. A second set of MRIs was obtained 4 to 6 months later if contrast-enhancing lesions (CELs) or swellings were seen on the first set of MRIs. MRI examinations were performed on a 1.5-T Signa unit (General

Electric, Milwaukee, WI). Brain MRI sequences included (i) fast spin echo (FSE) (proton density/T2-weighted images [T2WIs]) with a repetition time (TR) of 2000 to 4000 ms and echo time (TE) of 20 to 100 ms; (ii) fluid attenuated inversion recovery (FLAIR) with a TR of 10,000 ms, TE of 160 ms, and inversion time of 2000 to 2200 ms; and (iii) T1 SE WI with a TR of 400 to 600 ms and TE of 8 to 16 ms, which was obtained before and within 15 min after the intravenous (IV) administration of gadopentate dimeglumine (Magnevist; Berlex Labs, Cedar Knolls, NJ) at 0.1 mmol/kg. Axial contiguous slices of 3 mm thickness with 22 to 24 cm of field view were obtained for all the brain studies described above. Spinal cord MRIs included (i) routine sagital sequences of T1 and T2 pre- and postcontrast WIs on the entire spinal cord, and (ii) axial sequences as needed.

MRI analysis

MRIs were reviewed by a neuroradiologist (JB) and neurologist (FB). For brain MRI evaluations, a T2 lesion was defined as any hyperintensity that was more than 3 mm long within the plane of the brain MRI slice (Kuroda *et al*, 1995). A black hole (BH) was defined as a FLAIR/T2WI hyperintensity that was hypointense on the correspondent T1WI, and did not enhance when gadopentate dimeglumine was administered (Bagnato *et al*, 2003). Regions of dirty white matter (WM) (Fazekas *et al*, 1999) were defined as areas of diffusely increased signal intensity either among discrete lesions on T2 sequences or in the absence of any focal abnormality.

The sites of FLAIR/T2WI lesions were also classified as previously suggested (Fazekas *et al*, 1999). Lesion locations were defined as (i) within the brain stem or cerebellum (i.e., posterior fossa [PF]); (ii) abutting the lateral ventricles (i.e., periventricular [PV]); and (iii) adjacent to the cortex (i.e., juxtacortical [JC]). All other lesions were designated as discrete (D).

To measure lesion volumes, lesions were first traced on hardcopies. T2-hyperintense and T1-hypointese lesion volumes were then calculated using a semiautomated, local thresholding technique within the MEDx 3.42 visualization and analysis software (Medical Numerics, Sterling, VA; www.medicalnumerics.com). The lesion volumes were measured on computer-displayed images twice by the same observer (FB), with an intraobserver variability of approximately 3.0% (Gasperini *et al*, 2001). After identifying that one patient had T1-hypointense lesions, the patient's T1WI was registered upon the T2WI using FMRIB's (Functional Magnetic Resonance Imaging of the Brain Centre, University of Oxford, UK) linear image registration tool (FLIRT, version 3.1). (Jenkinson and Smith, 2001) This registration was performed to determine what proportion of the T2 lesion load corresponds to BHs in this patient.

Statistical analyses

Descriptive statistics were used to evaluate the clinical and MRI variables of the patient cohorts. Two-sample Kolmogorov-Smirnov tests were used to analyze differences in age, duration of disease, EDSS scores, and proviral loads among the cohorts of patients. Exact permutation tests were performed to evaluate differences in gender, ethnicity, clinical signs, and associated autoimmune disease frequencies among the same patient cohorts. Kendall's tau b (τ_b), a nonparametric measure of association that accounts for ties identified in our data set, was used to estimate the association between clinical and biological variables. All reported P values were based on two-tailed statistical tests, with a significance level of .05. The statistical analysis was performed using SPSS version 12.0 for the two-sample Komogorov-Smirnov tests and Kendall's τ_b, and StatXact version 5.0 for the exact permutation tests.

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