OCCULT DIFFUSE INVOLVEMENT OF SUPRATENTORIAL WHITE MATTER DETECTED BY MAGNETIC RESONANCE IMAGING IN HTLV-1 CARRIERS

SHINSUKE YAMAUCHI1, SHINJI IJICHI1, KIYOSHIGE NIINA2, YOICHI HOKEZU1, IKURO MARUYAMA1, TATSURU NIIMURA3 and MITSUHIRO OSAME1

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Abstract: We describe three human T lymphotropic virus type I (HTLV-1) carriers, who are characterized by a dissociation between the clinical features including scarce cognitive impairments and peculiar hyperintensities in the deep and subcortical white matter detected by T2-weighted magnetic resonance imaging (MRI) scans. Unlike spotty MRI findings which are encountered in clinically asymptomatic elderly individuals and are previously described in some HTLV-1 carriers, the MRI changes in our patients were diffuse and extensive. Known central nervous system disorders accompanying a cerebral white matter involvement were failed to be diagnosed. These findings support a possibility that extensive lesions in the supratentorial white matter are associated with HTLV-1 infection with minimal symptoms, and suggest that MRI scans may detect occult diffuse inflammatory changes associated with the virus infection in these patients.

Keywords: Human T lymphotropic virus type I (HTLV-1); Cerebral white matter; T2-weighted image; High intensity.

INTRODUCTION

Sustained prevalence of human T lymphotropic virus type I (HTLV-1), a member of the oncoviridae subfamily, is common in many parts of the tropics and in southern Japan (Osame and McArthur, 1992). The virus causes two well defined diseases: adult T cell leukemia/lymphoma, which is a neoplastic disease characterized by clonal expansion of HTLV-1-transformed T cells, and HTLV-1-associated myelopathy/ tropical spastic paraparesis (HAM/TSP). The latter is a non-fatal neurological syndrome characterized by predominant involvement of the spinal cord and manifested by chronic spastic paraparesis. Although cognitive impairment is included in less common neurological findings in this disease (Osame and McArthur, 1992), several necropsy studies have revealed that the critical pathological findings including mononuclear infiltration or perivascular cuffing, which is prominent in the thoracic spinal cord, are commonly seen in the cerebral white matter of HAM/TSP patients (Izumo et al., 1989). Cerebral white matter involvement detected by magnetic resonance imaging (MRI) has been reported in an HTLV-1 infected symptomless individual (Mattson et al., 1987) and the incidence of cerebral MRI abnormalities is significantly higher in patients with HAM/TSP than in the controls (Kira et al., 1988; Furukawa et al., 1989). These observations suggest that occult involvement of the cerebral white matter may be associated with HTLV-1 infection. In previous cerebral MRI studies on HTLV-1 infected individuals, common abnormal findings were multiple spotty high intensities in deep and subcortical areas on T2-weighted images (Kira et al., 1988; Furukawa et al., 1989). Moreover, diffuse white matter involvement detected by MRI was also described in connection with pyramidal tract signs and cognitive dysfunctions in patients with HAM/TSP (Natori, 1989; Valderrama et al., 1989; Uyama et al., 1991; Konagaya and Iida, 1991). Here we report three non-demented HTLV-1 carriers, whose cerebral MRI

1Third Department of Internal Medicine, Faculty of Medicine, Kagoshima University, Kagoshima; 2Division of Internal Medicine, Kagoshima City Hospital, Kagoshima; and 3Kagoshima Red Cross Hospital, Kagoshima, Japan
revealed diffuse and widely distributed white matter high intensity on T2-weighted scans, and two of whom were free from apparent features of pyramidal tract impairment.

**CASE REPORTS**

**Patient 1.** A 74-year old man presented with a 34-year history of slowly progressive gait disturbance. Neurological examinations revealed spastic paraparesis with brisk tendon reflexes and extensor plantar responses. Vibration sensation was decreased on both legs. The score of Mini-Mental Examination was 26/30. Routine laboratory examinations including coagulation studies were all within normal limits. Electroencephalogram (EEG) showed a poor organization and modulation. Myelography and myelo-computed tomography (CT) scans demonstrated the cervical ossification of posterior longitudinal ligament (OPLL) with canal stenosis. MRI scans revealed diffuse high intensity signals in the deep and subcortical white matter on T2-weighted images (Figure 1A).

**Patients 2.** A 86-year old woman with a history of atrial fibrillation and episodes of angina pectoris presented with a transient weakness of her right arm. Routine neurological examinations disclosed no abnormality. Her intelligence quotient (IQ) was 102 on the Wechsler adult Intelligence Scale (WAIS). Routine laboratory examinations including coagulation studies were within normal limits. The EEG record showed normal results. Cerebral CT scans revealed diffuse hypodensities in the deep white matter, and MRI scans demonstrated high intensity signals diffusely distributed in the white matter on T2-weighted images (Figure 1B).

**Patients 3.** A 73-year old woman with a history of hypertension presented with a hand tremor. Neurological examinations revealed mild bradykinesia, mild hyperreflexia without extensor plantar response, and orthostatic hypotension. Her IQ was 100 on the WAIS. Routine laboratory examinations including coagulation studies were within normal limits. Cerebral CT scans disclosed diffuse hypodensity in the deep white matter, and MRI scans revealed diffuse high intensity signals in the white matter on T2-weighted images (Figure 1C).

These 3 patients showed positive anti-HTLV-I antibody titers in serum (1: 512, 1: 2048, and 1: 65536, respectively), and in patient 3 the antibody was also detected in cerebrospinal fluid (CSF) (1: 2028) by particle agglutination (PA) method (Fujirebio). The CSFs obtained from patients 1 and 2 were negative for the
antibody (PA). Western blot analysis confirmed the presence of antibodies to HTLV-I antigens derived from MT-2 cell line in sera both as IgG and IgM in these three patients (data not shown). Oligo clonal IgG was detected in CSF from patient 3, but not in patients 1 and 2. The level of myelin basic protein in CSF and circulating adrenocorticotropic hormone was normal in these three patients. Anti-cardiolipin antibody (ACLA) was not detected in patient 1 and 2, but the patient 3 showed the increased serum ACLA level both as IgG and IgM (ELISA). The concentration of serum cholestanol was not increased in patient 1 and 3 (not tested in patient 2).

**DISCUSSION**

Cerebral MRI changes in the present cases were diffuse and extensive, unlike periventricular leukoaraiosis (caps and lining) and increased T2 signal spots in the deep white matter which are encountered in clinically asymptomatic elderly individuals (Shmidt et al., 1992). Two of these three patients have cerebrovascular risk factors including cardiac disease in patient 2 and hypertension and serum antcardiolipin antibody, which would enhance coagulation conditions, in patient 3. However, the occurrence of ischemia or expanded arteriosclerosis (i.e.Binswanger’s disease) distributed to all MRI-evident lesions can not be predicted from the clinical features in these cases. The diagnoses of central nervous system disorders including leukodystrophy, storage diseases, multiple sclerosis, systemic effect of metabolic abnormalities, and toxins, which show a cerebral white matter involvement and may be asymptomatic in early stages, can be excluded on the basis of laboratory examinations and clinical features. Although patient 1 has spastic paraparesis, the diagnosis of HAM/TSP is equivocal because of his possible manifestation of cervical OPLL.

The seropositivity for HTLV-I together with a dissociation between the minimal cognitive impairment and remarkable MRI abnormality in the cerebral hemisphere white matter is the common characteristic in our three patients. Similar cases exhibiting unpredictable white matter MRI lesions have previously described in patients with HAM/TSP (Natori, 1989; Valderrama et al., 1989; Uyama et al., 1991; Koyanagi and Iida, 1991), and a possible correlation between the lesions and cognitive impairments was discussed (Uyama et al., 1991). Therefore, the significance of this report involves not only a confirmation of the dissociation between cognitive functions and MRI findings in HTLV-I infected individuals but also a suggestion that the diffuse MRI abnormalities are not related to apparent pyramidal tract signs at least in some cases. These observations indicate that less symptomatic extensive lesions in the cerebral white matter may be associated with HTLV-I infection, and suggest that MRI scans may detect occult diffuse inflammatory change associated with the virus infection in these patients. However, it still remains to be elucidated that possible processes, which result in cerebral white matter abnormal findings on MRI scans with less correlation with cognitive impairment (Mirsen et al., 1991; Almkvist et al., 1992; Tupler et al., 1992), are facilitated by HTLV-I infection.

**REFERENCES**


