Incidence and Clinical Significances of Human T-cell Lymphotropic Virus Type I-Associated Myelopathy with T2 Hyperintensity on Spinal Magnetic Resonance Images

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Abstract

Objective To clarify the incidence and clinical significance of HTLV-I associated myelopathy/tropical spastic paraparesis (HAM/TSP) showing T2 hyperintensity in the spinal cord on magnetic resonance images (MRI).

Patients and Methods We reviewed the spinal cord MRI of 38 HAM/TSP patients and analyzed them in relation to clinical and laboratory findings. Analyzed data were: age at onset, disease duration, disability status, responsiveness to interferon therapy, brain abnormalities on MRI, serum anti-HTLV-I titers, and cerebrospinal fluid (CSF) findings.

Results MRI findings of the spinal cord were classified into 3 types, “normal” (n=22, 57.9%), “atrophy” (n=13, 34.2%) and “T2-hyperintensity” (n=3, 7.9%). Patients in the normal and atrophy types showed slowly progressive paraparesis. Significant differences were not found between the normal and atrophy types in any clinical or laboratory data, including disease duration, disability status and responsiveness to interferon-alpha therapy. Meanwhile, all patients showing T2-hyperintensity had severe paraparesis of a rapid progressive nature, with CSF IgG elevation.

Conclusion HAM/TSP with T2-hyperintensity on spinal MRI shows a rapid progressive clinical course with severe motor impairment. The incidence of this malignant form of HAM/TSP is estimated to be around 7.9%.

Key words: HTLV-I associated myelopathy, tropical spastic paraparesis, magnetic response imaging, spinal cord atrophy, T2-hyperintensity, myelitis


Introduction

Human T-lymphotropic virus type I (HTLV-I) -associated myelopathy/tropical spastic paraparesis (HAM/TSP) is a chronic progressive myelopathy occurring in HTLV-I carriers (1, 2). The pathology of HAM/TSP is characterized by atrophy of the thoracic cord associated with parenchymal degeneration and cellular infiltrates. This pathological change is demonstrated on magnetic resonance images (MRI) as thoracic cord atrophy without intensity changes (3-8). Recently, cases of HAM/TSP showing high signal intensity (T2-hyperintensity) without thoracic cord atrophy on T2-weighted MRI were reported (9-13). However, the incidence and clinical significance of these spinal cord abnormalities remains undetermined.

In order to clarify the incidence and clinical significance of spinal cord MRI abnormalities in HAM/TSP, we reviewed the spinal cord MRI of 38 HAM/TSP patients and analyzed the relation between their MRI abnormalities and...
clinical laboratory findings.

**Patients and Methods**

We studied 38 HAM/TSP patients who had had at least one MRI study performed on their brain and spinal cord. Informed consent for scientific research including the present study had been obtained from all patients. The diagnosis of HAM/TSP was made based on the WHO diagnostic guidelines for HAM/TSP (5). Anti-HTLV-I antibodies were measured by a routine particle agglutination method. In patients with T2-hyperintensity on spinal MRI, other possible causes of myelopathy such as multiple sclerosis, neurosarcoidosis, parasitic myelitis and collagen disease associated myelitis were excluded. The severity of spastic paraparesis was graded by scores on the Kurtzke’s Expanded Disability Status Scale (EDSS) (14). MRI studies were performed on 1.5 Tesla imagers (General Electric Medical Systems, MI) using spin echo short TR, short TE (TR=300, TE=16) and long TR, and long TE (TR=3500, TE=100/162) pulse sequences. Hard copy films of the spinal cord and brain MR images were examined in random order by a certified neuroradiologist without any knowledge of clinical and laboratory details. The ratio of the cross-sectional spinal cord area to the intrathecal area at the Th7 spine level was measured using Image J software (http://www.rsb.info.nih.gov/ij, version 1.37v). Clinical and laboratory parameters analyzed in this study were as follows: age at onset, disease duration, disability status, responsiveness to interferon-alpha therapy, brain abnormalities on MRI, serum anti-HTLV-I titers, and cerebrospinal fluid (CSF) findings.

For statistical analysis, we used the Mann-Whitney U test for comparisons of clinical parameters between the two groups and Kruskal-Wallis H test followed by a Dunn’s post-hoc test for comparisons of clinical parameters among the three groups. p<0.05 was considered as statistically significant.

**Results**

MRI findings of the spinal cord were classified into three types; “normal” (Fig. 1, A and B), “atrophy” (Fig. 1, C and D) and “T2-hyperintensity” (Fig. 2). In HAN/TSP patients judged as having spinal cord atrophy, the ratios of the cross-sectional spinal cord area to the intrathecal area at the Th7 spine level were less than 25% (mean: 18.9%, range: 14.5-22.9%).

Of the 38 patients, 22 patients (57.9%) had a normal spinal cord, 13 (34.2%) had thoracic cord atrophy and 3 (7.9%) had T2-hyperintensity. Details of spinal MRI findings in three patients of T2 hyperintensity type were as follows; T2 hyperintensity lesion at both cervical and thoracic cord levels (C3-Th12) with cord swelling but without gadolinium enhancement (Fig. 2, A, B and C), at the thoracic cord level (Th4-Th12) without cord swelling and gadolinium enhancement (Fig. 2, E and F), and at both cervical and high thoracic cord levels (C2-Th1) with both cord swelling and gadolinium enhancement (Fig. 2, H, I and J). Head MRI in all patients of T2 hyperintensity type showed small white matter lesions, but did not suggest plaques in multiple sclerosis (Fig. 2, D, G and K). The following autoantibodies were negative: anti-nuclear factor; rheumatoid factor; anti-double strand DNA antibody (Ab), anti-SS-A Ab, anti-SS-B Ab, anti-cardiolipin beta2GP1 Ab, anti-RNP Ab, PR3-ANCA and MPO-ANCA. Visual evoked potential latency was also normal in all 3 patients.

Clinical and laboratory details of the 3 types are shown in Table 1. Significant differences were not found in any clinical or laboratory variables between normal and atrophy groups. Although EDSS scores of less than 3.0 were more frequent in the normal group than in the atrophy group (Fig. 3, panel A), the mean EDSS score was not different between the two groups (Fig. 4). Spinal cord atrophy was also not associated with disease duration. A normal spinal cord on MRI was found in 8 patients with over 10 years of disease duration (Fig. 3 panel B), including 4 patients with over 20 years of disease duration. Clinical improvements of an EDSS score of more than 1.0 after 28 days’ intramuscular injections of 3M IU natural interferon-alpha were equally
Figure 2. MR images in the T2-hyperintensity type of HAM/TSP patients. Patient #1 (58-year-old female): Diffuse hyperintensity areas (arrows) were observed on T2-weighted images (A: sagittal image at the cervical spine, B: sagittal image at the thoracic spine, C: axial image of the cervical cord at the C7 spine level). D: Head MRI showed non-specific small white matter lesions on T2-weighted images. Patient #2 (69-year-old male): Diffuse hyperintensity areas (arrows) were observed on T2-weighted images (E: sagittal image, F: axial image of the thoracic cord at the Th8 spine level). G: Head MRI showed non-specific small white matter lesions on T2-weighted images. Patient #3 (51 years old, female): Diffuse hyperintensity areas (arrows) were observed on T2-weighted images (H: sagittal image at the cervical spine, I: axial image of the cervical cord at the C6 spine level). J: Fine gadolinium enhancement was observed at the same spine level shown in panel I. K: Head MRI showed non-specific small white matter lesions on T2-weighted images.

Figure 3. Relation between spinal cord MRI findings and clinical features. EDSS was varied in both normal and atrophy groups. However, all patients in the T-2 hyperintensity group had severe disability (panel A). Duration of illness was also varied in both normal and atrophy groups, although all patients in T-2 hyperintensity group visited a hospital within four months (panel B).

observed in both the normal and the atrophy groups (Table 1), indicating that the presence of spinal cord atrophy on MRI had little value in the prediction of efficacy of interferon-alpha therapy. Meanwhile, all 3 patients showing T2-hyperintensity on spinal MRI reached an EDSS score of more than 7.5 within a year after onset (Fig. 3). Increased CSF IgG levels and IgG index, considered to show the presence of active inflammation in the CSF, were observed in all 3 patients (Table 1).
Discussion

HAM/TSP shows both brain and spinal cord abnormalities on MRI (3-8, 15-17). In particular, thoracic cord atrophy without signal intensity changes on MRI is accepted to be characteristic of HAM/TSP, but its incidence was varied, ranging from 20% to 74% (6-8). Recently, cases of HAM/TSP showing T2-hyperintensity in the spinal cord were reported (9-13). To clarify the incidence and clinical significance, especially in patients with T2-hyperintensity on spinal MRI, here we reviewed spinal MRI of 38 HAM/TSP patients. Spinal MRI abnormalities were observed as follows: spinal cord atrophy without signal change in 13 patients (34.2%), and T2-hyperintensity in 3 patients (7.9%). It should be noted that this study included novel spinal MRI finding termed T2-hyperintensity, and enrolled a large number of patients in the endemic area than other reports had done. Thus, the present results would reflect the exact frequency of spinal cord MRI abnormalities in HAM/TSP.

The present study showed that spinal cord atrophy on spinal MRI has no association with any clinical or laboratory parameters. Considering that spinal cord atrophy on MRI in HAM/TSP patients did not indicate a poor paraparesis prognosis or poor responsiveness to interferon-alpha therapy, HAM/TSP is different from multiple sclerosis because the atrophy of the brain or the spinal cord in multiple sclerosis patients is positively associated with the severe disability and poor responsiveness to immunomodulatory therapies (18-23). This study also clarified that there was no association between disease duration and the development of spinal cord atrophy. There were four patients who showed normal spinal MRI more than 20 years after the onset of disease, implying that the spinal cord atrophy develops independent of the disease duration in HAM/TSP.

Meanwhile, patients with T2-hyperintensity on spinal MRI should be considered to have a malignant form of HAM/TSP. All 3 patients showing T2-hyperintensity showed severe paraparesis within less than a year after onset, and they have increased CSF IgG levels. The association of cord swelling or contrast enhancement with T2-hyperintensity suggests that the active inflammatory process was highly augmented in patients with T2-hyperintensity. Nakagawa et al (23) found 14 patients showing acute or subacute onset and rapid progression among 153 HAM/TSP patients. The incidence (9.2%) was similar to that of the T2-hyperintensity group (7.9%) in this study. Although MRI findings were not described in their report, the 14 patients were reported to have severe disability, marked spasticity and high CSF anti-HTLV-1 antibody titers (23). We also reported that HAM/TSP patients showing rapid progression have increased CSF IgG levels (24). Taken these findings together, it is assumed that a malignant form of HAM/TSP may exist in less than 10% of the patients and that T2-
hyperintensity or increased CSF IgG levels may become surrogate markers in this condition. Clinical significances such as rapid progression and CSF IgG elevation in HAM/TSP with T2-hyperintensity on spinal MRI were also observed in the reported HAM/TSP cases showing T-2 hyperintensity on spinal MRI (9-12). The question as to whether patients with T2-hyperintensity will finally show spinal cord atrophy on MRI should be elucidated. History of rapid deterioration was not obtained from any of the 13 patients showing the spinal cord atrophy on MRI, indicating that HAM/TSP showing T2-hyperintensity may develop underlying immunopathogenic mechanisms which differ from that showing spinal cord atrophy on MRI. More recently, chronic progressive HAM/TSP patients with T2-hyperintensity on spinal MRI were also reported (25, 26). Although it is likely that there are some more variations of spinal MRI findings in HAM/TSP, recognition of the clinical significance of the malignant form of HAM/TASP is important.

In conclusion, spinal MRI findings of HAM/TSP were classified into three types; normal, atrophy and T2-hyperintensity. The spinal cord atrophy on MRI had little value for the prediction of prognosis of disability or responsiveness to interferon-alpha therapy. In contrast, HAM/TSP with T2-hyperintensity on spinal MRI showed a rapid progressive clinical course with severe motor impairment with IgG elevation in CSF. The incidence of this malignant form of HAM/TSP is estimated to be approximately 7.9%.

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References

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