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HTLV-I-associated myelopathy: analysis of 213 patients based on clinical features and laboratory findings

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We studied the clinical features and laboratory findings in 213 patients with HTLV-I-associated myelopathy/tropical spastic paraparesis as diagnosed in Kagoshima University Hospital. Some aspects of clinical features in HTLV-I-associated myelopathy/tropical spastic paraparesis were characterized by mode of HTLV-I transmission and age of onset. The patients with onset after 15 years old and no history of blood transfusion before the onset of the disease (151 patients, group I) showed a shorter interval between the time of disease onset and that of inability to walk. The patients with onset before 15 years old and without history of blood transfusion (21 patients, group II) had short stature and slow progression of the disease. The interval time and the progression of the disease in patients with history of blood transfusion before onset of disease (41 patients, group III) were in between those of the above two groups. Patients whose ages of onset were older than 61 years old showed a faster progression than those with younger onset regardless of the mode of HTLV-I transmission. HTLV-I-associated myelopathy/tropical spastic paraparesis patients often also showed other organ disorders such as leukoencephalopathy (69%), abnormal findings on chest X-ray (50%), Sjögren syndrome (25%) and arthropathy (17%). The patients with low anti-HTLV-I antibody titers in the cerebrospinal fluid (2X–8X by PA method) had an older age of onset on average, milder clinical symptoms and lesser increase of neopterin in the cerebrospinal fluid than those in the high titer subgroup whose titers were higher than 1024X in cerebrospinal fluid regardless of the mode of HTLV-I transmission. We speculate that the clinical course of HTLV-I-associated myelopathy/tropical spastic paraparesis mainly shows a slow progression which consists of an initial progressive phase (probably an inflammatory phase) and a latter chronic phase, although some patients showed acute/subacute onset and rapid progression.

Keywords: HAM/TSP; clinical features; laboratory findings; complications; blood transfusion

Introduction

The association of spastic paraparesis with human T-lymphotropic virus type I (HTLV-I) was discovered in two different areas: the Caribbean basin and Japan (Gessain *et al*, 1985; Osame *et al*, 1986). Comparative analysis of HTLV-I-associated myelopathy (HAM) in Japan and HTLV-I-positive tropical spastic paraparesis (TSP) in the Caribbean basin revealed that the two diseases were essentially the same disorder (Roman and Osame 1988). Although the main neurological feature of HAM/TSP is myelopathy, some patients with this disorder have brain white matter lesions (Newton *et al*, 1987; Furukawa *et al*, 1989; Kira *et al*, 1991; Ogata *et al*, 1993), cerebellar symptoms (Roman and Roman 1988; Osame *et al*, 1990a), amyotorophic lateral sclerosis (ALS)-like features (Arimura *et al*, 1989; Vernant *et al*, 1989; Kuroda and Sugihara, 1991) or neuropathy (Arimura *et al*, 1987; Said *et al*, 1988). The disorders which have been discussed in association with HTLV-I include T-lymphocyte

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alveolitis (Sugimoto *et al*, 1987; Maruyama *et al*, 1988; Vernant *et al*, 1988), Sjögren syndrome (Vernant *et al*, 1988; Ijichi *et al*, 1991; Kanazawa *et al*, 1993; Kuroda *et al*, 1993), uveitis (Sasaki *et al*, 1989; Ohba *et al*, 1989; Hayasaka *et al*, 1991; Mochizuki *et al*, 1992), arthropathy (Kitajima *et al*, 1989; Nishioka *et al*, 1989; Eguchi *et al*, 1992), polymyositis (Morgan *et al*, 1989; Inose *et al*, 1992; Higuchi *et al*, 1993), thyroiditis (Fukuzawa *et al*, 1991), pseudohypoparathyroidism (Yoshida *et al*, 1993) and Behçet disease (Igakura *et al*, 1993; Kanazawa *et al*, 1993). Among the reported immunological abnormalities in HAM/TSP (Itoyama *et al*, 1988; Kitajima *et al*, 1988; Jacobson *et al*, 1990; Kuroda *et al*, 1991), the neopterin level is a useful parameter for the cell-mediated immune reaction in the cerebrospinal fluid (CSF) of HAM/TSP, because it is derived from macrophages stimulated by activated T cells (Nomoto *et al*, 1991; Ali *et al*, 1992). Despite significant advances in study of the pathophysiology of HAM/TSP (Shibasaki *et al*, 1988; Iwasaki, 1990; Jacobson *et al*, 1992; Furukawa *et al*, 1992; Iwasaki *et al*, 1992; Izumo *et al*, 1992; Umehara *et al*, 1993; Umehara *et al*, 1994a; Umehara *et al*, 1994b), development of a more effective therapy remains an urgent priority. In this paper we shall address and discuss the following problems: significant clinical and laboratory findings which serve to elucidate the pathomechanism of HAM/TSP, the clinical course of HAM/TSP, the clinical features of HAM/TSP characterized by the mode of transmission and age of onset, complications in HAM/TSP patients, correlation between the titer of anti-HTLV-I antibody in CSF and the clinical severity, and treatment strategies. The first patient with HAM/TSP was diagnosed in our University Hospital in 1985, and since then we have identified a further 213 patients. The clinical features and laboratory findings of these 213 patients were analyzed retrospectively to answer the above problems.

Results

Clinical findings

The male:female ratio was 1:2.21 in group I, 1:6.0 in group II and 1:1.73 in group III. The mean ages of onset were 46.0 years in group I, 10.7 years in group II and 50.9 years in group III. The mean interval between blood transfusion and onset of the disease

Table 1 Motor disability grading for HAM/TSP

Grade	*Motor disability*
0	Normal gait and running
1	Normal gait but runs slowly
2	Abnormal gait (staggering or spastic)
3	Abnormal gait and unable to run
4	Needs support while using stairs but walks without assistance
5	Needs one hand support in walking
6	Needs two hands support in walking
7	Unable to walk but can crawl with hands and knees
8	Unable to crawl but can turn sideways in bed
9	Unable to turn sideways but can move the toes
10	Completely bedridden

Table 2 Clinical findings in 213 patients with HAM/TSP -1-

	All Cases	*Group*			*P values*		
		I	*II*	*III*	*I vs II*	*I vs III*	*II vs III*
Number of patients	213	151	21	41			
Sex: male/female	65/148	47/104	3/18	15/26			
Age	59.3 ± 11.7* (29–86)**	59.0 ± 11.4 (29–86)	48.1 ± 11.6 (29–72)	66.1 ± 7.8 (53–83)	< 0.001	< 0.001	< 0.001
Age of onset	43.8 ± 17.4 (6–78)	46.0 ± 15.2 (17–78)	10.7 ± 3.5 (6–15)	50.9 ± 10.4 (28–68)	< 0.001	<0.045	< 0.001
Interval between blood transfusion and onset of disease (month)	–	–	–	88.3 ± 113.8 (0.25–420)			
Progression rate	0.61 ± 0.77	0.67 ± 0.84	0.14 ± 0.06	0.41 ± 0.38	0.004	0.057	0.002
Height (cm)	153 ± 8.7 (127–172)	153 ± 8.2 (135–172)	149 ± 10.9 (127–167)	156 ± 8.3 (140–172)	0.038	NS	0.015
Weight (kg)	50 ± 9.2 (27–76)	51 ± 9.1 (34–76)	45 ± 10.4 (27–64)	50 ± 8.2 (32–61)	0.031	NS	0.094

Group I: patients with adult onset (onset after 15 years old) and no history of blood transfusion before the onset of the disease
Group II: patients whose ages of onset were before 15 years old and who had no history of blood transfusion
Group III: patients who had history of blood transfusion before the onset of the disease
P values are calculated by two sample t test, χ^2 test or Fisher's exact probablility test. The values under 0.10 were shown. NS: not significant. * mean ± s.d., **range

Table 3 Clinical findings in 213 patients with HAM/TSP -2-

	All Cases	*Group*			*P values*		
		I	*II*	*III*	*I vs II*	*I vs III*	*II vs III*
Initial symptoms (%)							
Gait disturbance	65%	64	86	61	0.044	NS	0.046
Urinary disturbance	33	36	10	37	0.016	NS	0.024
Numbness of lower legs	13	12	0	24	0.084	0.045	0.010
Constipation	6	7	0	5			
Lumbago	9	10	10	2			
Hand tremor	3	4	0	2			
Disability grade[a]	4.6 ± 2.1* (0–10)**	4.5 ± 2.0 (0–10)	5.0 ± 1.9 (2–9)	4.7 ± 2.3 (0–9)			
More than grade 7	18.3%	15.9	23.8	24.4			
Interval between onset of disease and inability to walk	12.4 ± 10.7 (7days–35yrs)	8.3 ± 8.8 (7days–27yrs)	24.0 ± 10.3 (8–35yrs)	16.2 ± 10.2 (2–32yrs)	0.002	0.030	NS
Abnormality in brain MRI (%)	48/70 69%	35/50 70	5/8 63	8/12 75			
IQ (WAIS-R)	80.4 ± 12.9 (63–107)	83.1 ± 14.5 (63–107)	79.0 ± 3.6 (76–83)	73.7 ± 14.4 (63–90)			
Number of patients with low IQ[c]	8/15	4/9	2/3	2/3			

[a] For disability grading scale see Table 1
[b] Foe definition of the groups see Table 2
[c] Number of patients with low IQ (below 80)/patients studied
P values are calculated by two sample t test, χ^2 test or Fisher's exact probability test. The values under 0.10 were shown.
NS: not significant. * mean ± s.d., **range

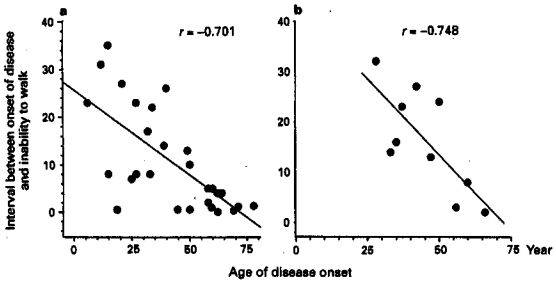

Figure 1 Interval between onset of disease and inability to walk was negatively correlated with the age of disease onset in group I + II (a) and group III (b).

Figure 2 The progression rate increased with the age of onset in groups I + II (a) and group III (b), and the progression rate increased with the age at first blood transfusion in group III (c).

in group III was 7.3 years, varying from one week to 35 years. The height percentile was significantly lower in group II when compared to the other groups ($P < 0.05$) (Table 2).

The major initial symptom was a gait disturbance (65%), followed by urinary disturbance in 33% of the patients. The mean motor disability grade was 4.6 (Table 3). Notably, 18.3% of these patients were unable to walk; this appeared from 7 days to 35 years after disease onset (mean ± s.d. = 12.4 ± 10.7 years). The interval between onset of disease and inability to walk was significantly shorter in group I than in the other groups (Table 3). The interval was negatively correlated with age of disease onset in all these groups (Figure 1).

The progression rate increased in patients with ages of onset after 61 years old and were significantly different in groups I and II compared to those patients under 60 years old ($P < 0.01$) (Figure 2a). The simple correlation coefficient between progression rate and age of onset in both groups was $r = 0.558$. In group III the progression rate increased with age of onset (Figure 1b) and the age at first blood transfusion (Figure 2c). A significant difference in progression rate was seen between patients with history of blood transfusion after 50 years old and patients with history of blood transfusion before 50 years old in this group ($P < 0.01$).

Table 4 Laboratory findings in 213 patients with HAM/TSP -1-

	All Cases	*Group*			*P values*
		I	*II*	*III*	*I vs II*
Number of patients	213	151	21	41	
Titers of anti-HTLV-I antibody[a]					
in serum	2^7-2^{20}	2^7-2^{20}	2^8-2^{18}	2^8-2^{16}	
in CSF	2^1-2^{22}	2^1-2^{22}	2^4-2^{11}	2^3-2^{12}	
White blood cells (/mm^3)	5654 ± 1863* (1900–11000)**	5655 ± 1862 (2700–10300)	5932 ± 2207 (2140–11000)	5500 ± 1693 (1900–9800)	
under 4500 mm^{-3}	33%	35	25	30	
Platelets 10^4 mm^{-3}	22.5 ± 7.3 (7.6–56.4)	22.1 ± 6.3 (9.8–46.9)	26.3 ± 10.7 (12.5–55.8)	22.1 ± 8.2 (7.6–56.4)	NS
under 13.0×10^4 mm^{-3}	5.7%	4.3	10.5	8.3	0.056
Ca [4.5-5.5mEq l^{-1}	4.5 ± 0.3 (3.8–6.2)	4.6 ± 0.3 (3.8–6.2)	4.4 ± 0.3 (3.9–5.2)	4.5 ± 0.3 (4–5.5)	NS
under 4.5mEq l^{-1}	40%	32	55	49	0.043
IgG [800-1800mg dl^{-1}	1842 ± 582 (684–5114)	1842 ± 608 (684–5114)	1849 ± 545 (921–2798)	1836 ± 512 (1111–3398)	
over 1800mg dl^{-1}	50%	50	56	47	
IgE [45-530u ml^{-1}	103 ± 248 (1–2540)	107 ± 277 (1–2540)	95 ± 196 (1–639)	92 ± 136 (1–421)	
under 45u ml^{-1}	57%	54	75	58	
IgD [0.3-4.0mg dl^{-1}	4.4 ± 7.5 (0.3–74)	4.7 ± 8.7 (0.3–74)	4.4 ± 5.0 (0.3–16.7)	3.3 ± 3.8 (0.3–17.3)	NS
over 4mg dl^{-1}	25%	24	38	26	0.073

[a] PA method
P values are from comparing Group I, and Group II calculated by two sample t test,
χ^2 test or Fisher's exact probability test. There was no significant difference between Groups I and III or Groups II and III. The values under 0.10 were shown
NS: not significant. * mean ± s.d., ** range
Normal range is given in square brackets

Laboratory findings

Tables 4 and 5 list the laboratory findings in HAM/TSP. Serum Ca levels were within lower limits of normal controls in groups I and III, and decreased in group II. The mean value of CD4/CD8 ratio was increased slightly in group III but the difference did not reach statistical significance.

White blood cell counts and platelets decreased in 33% and 5.7% of all patients, respectively. The serum IgG and IgD levels were increased while that of IgE decreased. IgE in serum tended to decrease with the disease duration ($P = 0.05$). Rheumatoid factor and antinuclear antibody were positive in 26% and 27% of all patients, respectively. With the exception of one patient, assays for other autoantibodies (ie anti-SS·A, SS·B and RNP antibodies) were negative. These findings were not significantly different between the three groups. No significant correlation was found between the duration of illness and titers of anti-HTLV-I antibody in either serum or CSF.

CSF findings

Neopterin in CSF increased in all three groups. There were no significant differences in the titers of anti-HTLV-I antibody, cell counts or IgG between each group (Table 5). Three patients had higher titers in CSF than in serum and all of these patients showed relatively rapid progression of their clinical symptoms. The level of neopterin was correlated with the titers of anti-HTLV-I antibody in CSF ($r = 0.472$).

Complications in patients with HAM/TSP

Half of the patients (63 in 126 patients) presented with abnormal findings on chest X-ray such as signs of interstitial fibrosis, chronic bronchitis, old tuberculosis and pleural effusion. These findings were confirmed in 25 of 40 patients examined by chest CT. In 30 patients who were examined by BAL, 20 of them had increased ratios of lymphocytes in BALF. Twenty-five percent of patients had Sjögren syndrome, 21.2% had cataract, 17.3% had arthropathy, 15.4% had glucose intolerance and 3.8% had

uveitis (Table 6).

In 68 patients who had undergone T2-weighted brain MRI, multiple high intensity areas in the white matter were found in 47 (69%) (Figure 3). Lesions were present in both subcortical white matter and periventricular area. Eight patients showed a diffuse white matter lesion comparable to leukoariosis on the brain MRI. None of the white matter lesions were enhanced by gadlinium in five patients except one who had meningoencephalitis. These findings were most frequent in patients in their 50s (79%) although the distribution was considerably even (Table 7). The incidence of these complications was not different among the three groups.

Eight of 15 patients studied by WAIS-R had low IQs, ranging from 63 to 78 (mean ± SD = 70.9 ± 6.2). All of these eight patients showed multiple abnormal high intensity areas in white matter on T2-weighted MRI. The brain MRI findings ranged from small high intensity spots to diffuse lesions in white matter. These findings were not different between the three groups, although the number of patients studied was few (Table 3).

Rare complications included thyroid disorders in seven patients (three patients were suspected as having chronic thyroiditis, three patients with hyperthyroidism, one patient with hypothyroidism), myositis in six patients (detailed data reported by Inose *et al*) (Inose *et al*, 1992), and M-proteinemia in four patients (two of whom had multiple myeloma). Three patients with pseudohypoparathyroidism (detailed data reported by Yoshida *et al*) (Yoshida *et al*, 1993) were seen in group II. One patient had both Behçet disease and Sjögren syndrome (detailed data reported by Kanazawa *et al*) (Kanzawa *et al*, 1993). As a detailed search for these complications has not been performed in all of the 213 patients, the actual number of patients with these complications might even be higher.

Electrophysiological studies suggested that subclinical abnormalities in peripheral nerves were present in 43.7% of patients with HAM/TSP. Only one patient had definite clinical polyneuropathy. Three patients had clinical symptoms similar to ALS; however, they also had mild sensory polyneuropathy detected electrophysiologically.

A total of 20 patients died during the 5-year follow-up period, eight of whom had a history of blood transfusion. Table 8 summarizes their causes of death. Thirty per cent died of pulmonary disease other than malignancy. The majority of these pul-

Table 5 Laboratory findings in 213 patients with HAM/TSP -2-

	All Cases	*Group*		
		I	*II*	*III*
$CD4^+$ T cells (%)	43.0 ± 9.5* (21.4–63.8)**	43.2 ± 9.6 (21.4–63.4)	40.2 ± 9.1 (23.1–52.9)	43.9 ± 9.1 (27.9–63.8)
$CD8^+$ T cells (%)	29.2 ± 9.0 (11.3–50.4)	29.6 ± 8.9 (13.8–50.4)	29.2 ± 7.0 (14.2–39.3)	26.9 ± 10.7 (11.3–47.1)
CD4/CD8 ratio	1.68 ± 0.86 (0.33–5.60)	1.63 ± 0.75 (0.33–3.91)	1.54 ± 0.68 (0.66–3.01)	2.04 ± 1.31 (0.81–5.60)
RA factor[a]	26%	25	14	33
Antinuclear antibody[a]	27%	26	23	32
In CSF				
Titers of anti HTLV-I antibody[b]	2^1-2^{22}	2^1-2^{22}	2^4-2^{11}	2^3-2^{12}
Number of cells[c]	6.4 ± 14.2 (0–122)	7.4 ± 16.4 (0–122)	3.0 ± 2.0 (0–7)	4.5 ± 6.6 (0–39)
over 10 cells mm^{-3}	10%	12	0	11
IgG[d]	6.3 ± 6.2 (1–47.5)	6.8 ± 7.2 (1.8–47.5)	4.3 ± 1.7 (2.4–7.0)	5.3 ± 3.3 (1–12.3)
over 5 mg dl^{-1}	36%	38	25	38
Neopterin[e]	102.2 ± 113.8 (7.1–557.9)	116.2 ± 127.2 (7.1–557.9)	57.4 ± 43.4 (26.9–133.2)	68.0 ± 57.8 (16.6–198.1)
over 30 pmol ml^{-1}	71%	73	80	63

[a] Incidence of positivity in the patients,
[b] PA method,
[c] Normal: below 5 cells mm^{-3},
[d] Normal: below 5mg dl^{-1},
[e] Normal: below 30pmol ml^{-1},
There was no significant difference between the groups. *mean ± s.d., **range

Table 6 Complications in HAM/TSP

Cerebral white matter lesions in MRI	69%
Abnormal findings on chest radiograph	50%
Sjøgren syndrome	25%
Cataract	21%
Arthropathy	17%
Glucose intolerance	15%
Uveitis	4%

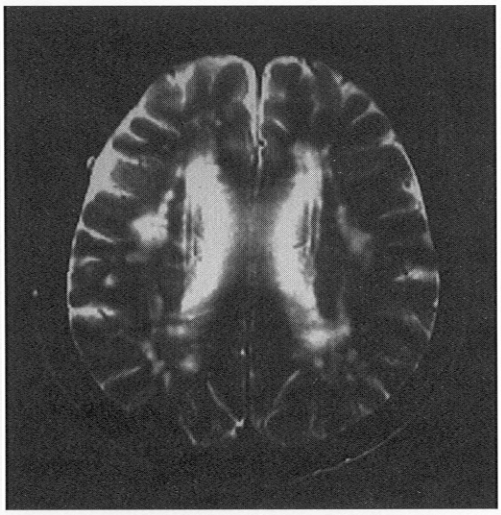

Figure 3 Multiple white matter lesions were demonstrated on brain MRI in a 66-year-old female HAM/TSP patient whose age of onset was 6 years. Her motor disability grade was 5 and her IQ was 76. The lesions were present in both the subcortical and periventricular white matter (Spin-echo, TR = 2000ms, TE = 90ms, Siemens Magnetom, 1.5 tesla)

Table 7 MRI abnormality and ageing

Age (year)	*Cases*	*%*
< 40	0/1	0
40–49	4/6	67
50–59	15/19	79
60–69	18/26	69
70 <	10/16	63
Total	47/68	69

Table 8 Summary of 20 deceased patients with HAM/TSP

Male/female	7/13
Age of death	
mean ± s.d.	62.5 ± 9.3years
range	42–77years
History of blood transfusion	8 cases (40%)
Duration of illness	
mean ± s.d.	11.4 ± 110.8years
range	9months–41years
Complications	
Carcinoma	5 cases
Leukemia	3
Lymphoma	1
Pneumonia	5
Pulmonary TB	1
Stroke	2
Others	3

monary diseases were comprised of interstitial pneumonia and coexisted with bacterial infection in the end stage of their life. There seemed to be no correlation between the motor disability of HAM/TSP and these complications.

Subgroup of acute progression in group I
Motor disability of 14 patients in group I was deteriorated more than three grades within 2 years before our first examination (acute progression subgroup). Motor disability and spasticity of legs were significantly severe in this subgroup. The antibody titers and neopterin in CSF were significantly increased in these patients (Table 9).

Subgroup of low CSF Anti-HTLV-I antibody titers
We compared the clinical symptoms and laboratory findings of patients whose CSF anti-HTLV-I antibody titers were positive by the Western blot method but had low values by the PA method (2X–8X). Twenty-two patients (15 in group I, 7 in group III) were segregated as a low titer subgroup. They were compared with the high titer subgroup (38 patients; 27 in group I, 6 in group II, 5 in group III) whose titers of anti-HTLV-I antibody in the CSF were higher than 1024X by the PA method. Significant differences were detected with regard to age of onset, duration of illness, positivity of Babinski's reflex, urinary disturbance, serum IgG and neopterin in CSF. The motor disability grades in the low titer group were milder than those of the patients with high titers, but did not reach statistical significance (Table 10). The following complications were seen in these 22 patients: abnormal findings on chest radiograph (6), cataracts (5), Sjögren syndrome (4), glucose intolerance (4), arthropathy (3), thyroid disorders (3) and myositis (2).

Discussion

In our initial study of HAM/TSP, we reported that the onset of HAM/TSP is insidious and clinical symptoms were slowly progressive (Osame *et al*, 1987; Osame *et al*, 1990a). Although this is essentially true, our present data showed that there were patients with acute/subacute onset and their clinical course was not the same. Interestingly, motor disability deteriorated rapidly in patients with late onset regardless of mode of HTLV-I transmission. In group III, motor disability deteriorated rapidly in patients with not only late onset but also older patients who received blood transfusion. The rapid progression of clinical symptoms in these elderly patients might be due to impairment of the immune surveillance system associated with aging (Utsuyama *et al*, 1992), the vulnerability of the nervous system with aging, or increased proliferation of HTLV-I.

Pathological study of the spinal cord in HAM/TSP clearly showed mononuclear cell infil-

Table 9 Comparison of patients with acute and slow progression in group 1

	Slow progression	*Acute progression*	*P value*
No of patients	137	14	
Age (mean)	58.6y	62.6	NS
Age of onset (mean)	45.3y	52.6	0.086
Disability grade (mean)	4.3	5.7	0.015
over grade 7 (%)	14.6%	28.6	0.049
Positive Babinski reflex	89%	100	NS
Ankle clonus	51%	75	NS
Spasticity of legs	77%	100	0.039
Urinary disturbance	90%	93	NS
Constipation	79%	92	NS
Sensory disturbance	67%	86	NS
Abnormality on brain MRI	67%	86	NS
Titers of anti-HTLV-I antibody in CSF (mean)[a]	$2^{6.95}$	$2^{9.14}$	0.007
Neopterin in CSF (mean)[b]	97.8	233.6	0.003

[a]: PA method
[b]: Values of neopterin are expressed as pmol ml^{-1}
P values were calculated by two sample t test, χ^2 test or Fisher's exact probability test
P values under 0.10 are shown
NS: not significant

Table 10 Comparison of clinical findings between two HAM/TSP groups of low and high anti-HTLV-I antibody titers in CSF

Titers in CSF	*≧ 1024 ×*	*≦ 8 ×*	*P value*
Number of patients	38	22	
Age	59.7 ± 12.8* (31–86)**	65.2 ± 9.9 (35–80)	0.087
Age of onset	45.8 ± 19.5 (6–78)	56.2 ± 10.0 (24–68)	0.025
Progression rate	0.84 ± 1.07 (0–5)	0.84 ± 0.98 (0–4)	NS
Disability grade	5.0 ± 2.1 (0–10)	4.0 ± 2.3 (0–8)	0.09
more than grade 7	21.1%	19.0	NS
Clinical symptoms			
Increased PTR	97%	91	NS
Babinski positive	95%	64	0.002
Urinary disturbance	100%	81	0.006
Constipation	89%	75	NS
Sensory disturbance	70%	65	NS
Laboratory findings			
Serum IgG	2128 ± 764	1602 ± 323	0.014
IgE	221 ± 498	52 ± 101	NS
IgD	3.6 ± 3.7	5.5 ± 6.7	NS
CSF neopterin	162 ± 162	41 ± 37	0.013
IgG	7.8 ± 4.0	7.6 ± 12.9	NS
cells ($/m^3$)	10.1 ± 18.8	8.5 ± 27.6	NS

PTR: patellar tendon reflex
P values are calculated by two sample t test, χ^2 test or Fisher's exact probability test. P values under 0.10 were shown
*mean ± s.d. (year), ** range

tration around small vessels. These cells were immunopositive with anti-CD4 and CD8 antibodies and the number of infiltrated cells and ratio of $CD4^+$ cells/$CD8^+$ cells declined with the duration of illness (Iwasaki *et al*, 1992; Izumo *et al*, 1992; Umehara *et al*, 1993). These pathological findings

suggest that there is an inflammatory response in the spinal cord of HAM/TSP patients (Iwasaki, 1990; Ijichi *et al*, 1993b; Umehara *et al*, 1994a; Umehara *et al*, 1994b). Fourteen patients with acute progression of symptoms in group I may reflect the inflammatory process related to the cell-mediated immune system occurring in the spinal cord, because they had high anti-HTLV-I titers and neopterin levels in CSF. Although all of the patients in group II were thought to be in the chronic phase, neopterin in their CSF was mildly elevated, suggesting the presence of mild but persistent inflammation even in the chronic phase. Along with the clinical course, the titers in serum were slightly increased, whereas the titers in CSF were decreased. The variation of titers and neopterin level in the CSF suggests that the immunological reaction continues in HAM/TSP (Mori *et al*, 1988; Ijichi *et al*, 1989). On the basis of these clinical and laboratory findings, the inflammatory process in the CSF or spinal cord might continue and then gradually subside in most patients with HAM/TSP. The clinical course of HAM/TSP appears to consist of an initial progressive phase (probably an inflammatory phase) and a chronic phase. Few patients show recurrence of the inflammatory phase similar to multiple sclerosis (MS) where exacerbations occur (Tashiro *et al*, 1989; Smith *et al*, 1992), though the clinical features of HAM/TSP are distinguished from those of multiple sclerosis by statistical multivariate analysis (Kubota *et al*, 1992).

The route of transmission in group III was mainly through blood transfusion as shown in the nationwide study of HAM/TSP in Japan (Osame *et al*, 1990b) and other countries (Gessain and Gout, 1992). Of the 172 patients who had no history of previous blood transfusion, the route of HTLV-I infection in group II may be postnatal transmission via breast milk, intrauterine infection or some unknown routes (Tsuji *et al*, 1990). The routes of transmission in the remaining 151 patients, group I, may be either horizontal transmission (husband → wife) of HTLV-I or vertical transmission (mother → child). Clinical aspects which were different in the three groups might be due to different modes of HTLV-I transmission.

Although immunological abnormalities in HAM/TSP have been reported (Kitajima *et al*, 1988; Mori *et al*, 1988; Jacobson *et al*, 1990), we confirmed the findings of increased serum IgG level and decreased IgE level. These laboratory findings were not significantly different between the three groups.

White matter lesions were detected on T2-weighted brain MRI in 69% of patients. The lesions were not enhanced by gadolinium and did not fluctuate as observed in MS. Although some of these lesions may be due to aging of the brain (Hunt *et al*, 1989), most of the abnormal findings on MRI could be related to HTLV-I infection because 60% of patients in their 40s showed white matter lesions on MRI. Our findings further confirmed the previous reports on MRI of HAM/TSP (Newton *et al*, 1987; Furukawa *et al*, 1989; Kira *et al*, 1991; Ogata *et al*, 1993). Only one patient has been reported regarding the possible association of dementia with HTLV-I infection (Lycke *et al*, 1993). The findings that a significant number of patients had low IQs and all of these patients had white matter lesions on MRI in our study suggest that mild subcortical dementia exists at least in some patients with HAM/TSP.

Half of our patients with HAM/TSP showed abnormal findings on chest radiograph. The increased ratio of T lymphocytes in BALF suggests that lung diseases in HAM/TSP patients may be caused by infiltrated T-lymphocytes (Sugimoto *et al*, 1987; Maruyama *et al*, 1988; Vernant *et al*, 1988).

The occurrence of autoimmune disorders in HAM/TSP patients has been reported (Vernant *et al*, 1988; Fukuzawa *et al*, 1991; Kanazawa *et al*, 1993; Kuroda *et al*, 1993). In our study, Sjögren syndrome was found in 25% of HAM/TSP patients but antibodies to SS·A and SS·B were positive in only one patient. Biopsy findings of the salivary gland showed infiltration of T lymphocytes (Ijichi *et al*, 1991). We speculate that Sjögren syndrome in HAM/TSP is an HTLV-I related subtype of Sjögren syndrome. One 71-year-old female patient with HAM/TSP had Behçet's disease and Sjögren syndrome (Kanazawa *et al*, 1993). We analysed sera of 28 patients with Behçet's disease and nine of them had anti-HTLV-I antibody (Igakura *et al*, 1993). This suggests that HTLV-I mimics or causes Behçet's disease. Arthropathy was present in 17% and rheumatoid factor was also positive in 26% of HAM/TSP patients. It has been reported that HTLV-I infects synovial cells (Kitajima *et al*, 1991), and that inflammatory arthropathy is induced in mice transgenic for HTLV-I pX gene (Iwakura *et al*, 1991). The arthropathy in HAM/TSP may be caused by HTLV-I infection (Kitajima *et al*, 1989; Nishioka *et al*, 1989; Ijichi *et al*, 1990; Sowa, 1992; Eguchi *et al*, 1992).

Electrophysiological and histological studies revealed peripheral nerve involvement in some of the HAM/TSP patients but the extent was relatively mild (Said *et al*, 1988; Arimura *et al*, 1989). In this study, only one patient showed clinical and physiological evidence of demyelinating polyneuropathy. Three patients showed clinical symptoms very similar to ALS, but they had mild polyneuropathy. An autopsy case of HAM/TSP presenting with ALS-like manifestations was reported by Kuroda and Sugihara (Kuroda and Sugihara, 1991). Prominent infiltration of inflammatory cells was found not only in the pyramidal tracts and anterior horn cells but also in all the degenerative areas. HAM/TSP should be considered in the differential diagnosis of ALS in patients with seropositivity to HTLV-I. The clinical phenotype of HAM/TSP regarding peripheral nerve involvement probably varies from an ALS-

like syndrome to a demyelinating polyneuropathy type.

In the present study some HAM/TSP patients exhibited uveitis or retinal vasculitis (Sasaki *et al*, 1989; Ohba *et al*, 1989; Hayasaka *et al*, 1991; Mochizuki *et al*, 1992), thyroid disorders (Fukuzawa *et al*, 1991) and myositis (Morgan *et al*, 1989; Inose *et al*, 1992; Higuchi *et al*, 1993). These complications might be related to a direct infection of HTLV-I or an impaired immune system by HTLV-I infection (Taguchi *et al*, 1991). Further investigations are needed to clarify their relationships to HTLV-I infection.

In group II the height significantly decreased, half of the patients had lower serum Ca level and three patients had pseudohypoparathyroidism (Yoshida *et al*, 1993). Several possibilities may explain the short stature in group II. They may have parathyroid dysfunction or genetic abnormality related to hypoparathyroidism. HTLV-I infection may affect growth because all of these patients had early onset of HAM/TSP, although human growth hormone (HGH) level was normal and results of HGH stimulation tests were variable in the patients studied (Yoshida *et al*, 1993).

Fatal complications such as malignancy and severe pneumonia may affect the prognosis of HAM/TSP, and these complications might be related to HTLV-I infection. We have to pay attention to these complications in follow-up analysis of HAM/TSP patients.

Patients with low anti-HTLV-I antibody titers in CSF showed later onset of disease and rather milder clinical findings as myelopathy than those of the high titer group regardless of the mode of HTLV-I transmission. The low titers and the low level of neopterin in CSF in these patients suggest that cell-mediated immune reaction in CSF is milder than that in the high titer subgroup. These patients may be at an early stage or have a milder form of HAM/TSP. Follow-up study is essential to determine whether clinical symptoms of these patients will progress to those observed in other HAM/TSP patients.

In conclusion, the observations made in these 213 patients with HAM/TSP suggest that HAM/TSP is a chronic, inflammatory disease of the spinal cord with some associated immunological abnormalities. Our study also suggests that HAM/TSP is a systemic disorder caused by HTLV-I. With regard to therapy for HAM/TSP, treatment strategies should be directed to antiviral and immunosuppressive regimens without any severe adverse effects. Ideal methods to treat HAM/TSP may be to disturb the infection and proliferation of HTLV-I, to disturb adhesion of the activated T cells to endothelium in the vessels, to remove HTLV-I-infected T cells from the peripheral blood and to suppress the inflammatory reaction in the spinal cord.

A rat model of HAM/TSP has recently been developed by Ishiguro *et al* (Ishiguro *et al*, 1992). Although pathological findings in the spinal cord were rather different from those in human HAM/TSP, ie no cell infiltration around small vessels in spinal cord and no increase of anti-HTLV-I-antibody in CSF, intensive study of the rat model could provide more insight into the pathomechanism of human HAM/TSP.

Materials and methods

We included in this study 213 patients with HAM/TSP whom we examined in Kagoshima University and whose diagnoses were made based on the World Health Organization diagnostic guidelines for HAM/TSP(Osame, 1991). Anti-HTLV-I antibodies were detected by enzyme-linked immunosorbent assay (ELISA) or particle agglutination (PA) methods (Fijirebio Inc, Tokyo, Japan) (Osame *et al*, 1987) and confirmed by Western blot analysis in all patients. DNAs from peripheral blood mononuclear cells of 40 of these 213 patients sampled at random were also analyzed by the polymerase chain reaction and confirmed to certain the provirus of only HTLV-I and not HTLV-II (Ijichi *et al*, 1993a). Based on the previously reported clinical and laboratory findings in HAM/TSP, the following factors in the 213 patients were subjected to computer analysis: clinical history of patients, neurological findings, electrophysiological findings, ophthalmological findings, titers of anti-HTLV-I antibody, white blood cells, platelets, calcium(Ca), phosphate(P), immunoglobulin(IgG, IgD, IgE), CD4 T cells, $CD8^+$ T cells, autoantibodies (rheumatoid factor, antinuclear antibody, anti-ribonucleoprotein (RNP) antibody, anti-SS·A antibody, anti-SS·B antibody), fasting blood sugar (FBS), oral glucose tolerance test, cerebrospinal fluid findings (number of cells, IgG, neopterin, titers of anti-HTLV-I antibody), brain and spinal cord magnetic resonance imaging (MRI) using a 1.5 tesla Siemens Magnetom or a 1.5 tesla General Electric Signa magnetic imaging system, Wechsler Adult Intelligence Scale-revision (WAIS-R), cause of death, chest X-ray and CT findings, bronchoalveolar lavage fluid (BALF) findings, bone radiograph findings, technetium 99 bone scintigraphy to detect accumulation of the radioisotope in joints, thyroid function, parathyroid function and salivary gland function. The significance of differences were determined by two sample t test, χ^2 test or Fisher's exact probability test. We set the level of statistical significance for P value at less than 0.05. Based on the history of blood transfusion and the age of onset, the 213 patients with HAM/TSP were divided into three groups as follows: group I, patients whose age of onset was after 15 years old and who had no history of blood transfusion before onset of the disease (n = 151 or 71%); group II, patients whose age of onset was before 15 years old and who had no history of blood transfu-

sion (n = 21 or 10%); group III, patients who had a history of blood transfusion before onset of the disease (n = 41 or 19%). The age of disease onset in this group III was after 15 years old in all patients.

As the main clinical feature in HAM/TSP is bilateral motor dysfunction in the lower legs, motor disabilities were graded as shown in Table 1. The progression rate was calculated by dividing disability grade by the duration of illness.

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