

# HTLV-1-associated myelopathy/tropical spastic paraparesis with pseudohypoparathyroidism

**Article abstract**—In many short-stature patients with human T-lymphotropic virus type I-associated myelopathy/tropical spastic paraparesis (HAM/TSP), signs and symptoms were manifested during childhood. Successive investigations revealed 12 of 14 short-stature patients with pseudohypoparathyroidism (PHP) from the findings of short metacarpi, parathyroid hormone infusion test, immunoblotting of erythrocyte membrane, or lymphocytic Northern blotting of  $G_{\alpha}$ . Patients with PHP probably showed HAM/TSP based on their modified immunologic status. Human T-lymphotropic virus type I infection did not induce PHP, but PHP may be a risk factor for the occurrence of HAM/TSP.

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Human T-lymphotropic virus type I– (HTLV-I–) associated myelopathy/tropical spastic paraparesis (HAM/TSP) is a chronic, slowly progressive myelopathy caused by HTLV-I. The main neurologic findings are spastic paraparesis and urinary disturbance. The incidence of HAM/TSP among HTLV-I–infected individuals is estimated to be less than 1%.<sup>1</sup> This suggests that occurrence of HAM/TSP requires additional factors, such as viral factors and host conditions.

Among 213 patients with HAM/TSP diagnosed at our university before 1993, 172 patients had no history of blood transfusion. Although HTLV-I was mainly transmitted by maternal milk, 151 patients did not begin to show symptoms of HAM/TSP until middle or old age. However, 21 of 213 patients presented symptoms at less than 15 years of age. These juvenile-onset patients appeared to have characteristic signs of short stature and hypocalcemia. Among them, three juvenile-onset patients with HAM/TSP and pseudohypoparathyroidism type Ia (PHP Ia) have already been reported.<sup>2</sup>

The purpose of the current study was to clarify whether short-stature patients with HAM/TSP had a tendency to exhibit signs and symptoms during early age and whether this was related to PHP Ia.

**Methods.** HAM/TSP was diagnosed according to World Health Organization diagnostic guidelines. We classified the heights of HAM/TSP patients using the table of Japanese average height against sex and ages (1995), and we examined 14 patients with HAM/TSP complicated with short stature for PHP Ia (table 1). We applied the following criteria for diagnosis of PHP Ia: 1) serum levels of calcium, phosphorus, and parathyroid hormone (PTH); 2) short stature, round face, obesity, slight mental retardation, and short metacarpi—signs of Albright's hereditary osteodystrophy (AHO); 3) resistance to PTH loading test (Ellsworth–Howard test, E-H test); and 4)  $\alpha$ -subunit of the

stimulatory guanine nucleotide-binding protein ( $G_{\alpha}$ ) abnormality. We used the Wechsler Adult Intelligence Scale (WAIS) to determine IQ.

The renal resistance for external PTH was examined from urinary cAMP excretion in response to 100 units of human recombinant PTH 1–34 (Asahi Chemical Ind., Tokyo, Japan) (E-H test). We set a  $<1 \mu\text{mol}$  increase of urinary excretion after PTH injection for 1 hour as positive. Erythrocyte membrane prepared by Dodge's procedure was subjected to 10% sodium dodecyl sulfate polyacrylamide gel electrophoresis and transferred to a nitrocellulose membrane. Western blotting was conducted with anti- $G_{\alpha}$  antibody (K-20 antibody; Santa Cruz Biotechnology, Inc., Santa Cruz, CA) and peroxidase conjugated rabbit anti-IgG antibody (Jackson Immunoresearch Laboratories, West Grove, PA) as a secondary antibody.

Twenty milliliters of heparinized blood was collected with the patient's permission, and lymphocytes were separated using a Ficoll-Hypaque solution (Mono-Poly Resolving Medium; Dainippon Pharmaceutical Co., Osaka, Japan). Total cellular RNA was extracted with 1 mL of RNazol B (Cinna Biotech, Houston, TX) per  $10^6$ . Five micrograms of RNA were subjected to Northern blotting with a [ $^{32}\text{P}$ ]-labeled  $G_{\alpha}$  cDNA.

**Results.** Among the 294 patients with HAM/TSP who were examined before 1995, 51 were found to have short stature (less than  $-1 \times \text{SD}$  against Japanese average height). Among them, 34 were adult-onset patients and 17 were juvenile-onset patients. Furthermore, among the short-stature patients measured against Japanese average height, the rate of juvenile-onset patients was significantly higher (table 2). The short-stature patients tended to manifest the signs and symptoms during early age.

Twenty-nine patients with juvenile-onset HAM/TSP (4 men, 25 women) were identified among the 294 patients with HAM/TSP. Their heights are plotted in the figure. These findings show that juvenile-onset patients were mainly those with short stature.

The clinical features of 14 short-stature patients with HAM/TSP are shown in table 1. Neither round face nor obesity was found in these patients. A younger brother of Patient 14 (aged 44 years, height 150 cm [ $-3.3 \times \text{SD}$ ]) and two sisters of Patient 2 had HAM/TSP and short stature; however, extensive examination was not allowed.

The immunoreactivity of  $G_{\alpha}$ , the 45 kDa molecular weight of human erythrocyte membrane,<sup>3</sup> was reduced in 11 patients and in the youngest sister (aged 38 years,

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**Table 1** Clinical and laboratory findings of the short stature patients with human T-lymphotrophic virus type 1-(HTLV-1-) associated myelopathy/tropical spastic paraparesis

Patient no.	Age, y/sex	Height, cm (SD)*	Age at onset	HTLV-1 titer†		Ca (8.5–10.5 mg/dL)	P (2.5–4.5 mg/dL)	HS-PTH (160–520 pg/mL)	1,25 (OH) <sub>2</sub> D <sub>3</sub> (20–76 mg/dL)	E-H test	Short meta-carpus	WAIS IQ	RBC Gsα	Lymphocytic		Diagnosis
				Serum	CSF									Gsα	mRNA	
1	57/F	140 (–2.4)	Childhood	2048	32	9.0	3.7	200	ND	ND	–	ND	Decreased	ND	PPHP	
2	72/F	134 (–2.8)	Infancy	8192	128	8.5	4.4	270	18.3	Positive	+	76	Decreased	ND	PHP Ia	
3	53/F	140 (–3.0)	Childhood	2048	252	8.8	4.1	340	58	Positive	+	83	Decreased	Decreased	PHP Ia	
4	71/F	137 (–2.2)	59 y	131,072	131,072	8.1	4.2	290	ND	Positive	–	82	Decreased	Decreased	PHP Ia	
5	49/F	144 (–2.2)	Childhood	32,768	512	8.4	3.7	300	ND	Negative	+	62	Decreased	ND	PHP Ia	
6	70/F	138 (–2.0)	66 y	2048	8	8.4	3.5	310	ND	ND	–	ND	Decreased	ND	PHP Ia	
7	44/M	149 (–3.4)	Childhood	65,536	128	8.4	2.9	360	16	ND	–	69	Decreased	Decreased	PPHP	
8	75/F	131 (–2.7)	60 y	8192	512	8.6	3.7	250	28.5	Negative	+	ND	Decreased	ND	PPHP	
9	18/F	132 (–4.9)	15 y	4096	128	8.6	5.4	ND	36.8	ND	–	ND	Decreased	ND	PPHP	
10	27/F	146 (–2.5)	13 y	8192	512	8.6	3.8	330	ND	Negative	–	56	Normal	ND		
11	42/F	140 (–3.1)	10 y	65,536	>4,092	9.4	3.9	320	ND	ND	–	ND	Normal	Normal		
12	50/F	143 (–2.4)	35 y	8192	64	8.0	3.2	ND	ND	ND	–	65	Decreased	ND	PHP Ia	
13	67/F	143 (–1.2)	30 y	4096	256	8.2	3.1	410	55	Negative	–	ND	ND	Decreased	PHP Ia	
14	47/F	127 (–5.5)	Childhood	2048	256	8.6	3.7	950	16.5	Positive	+	78	ND	ND	PHP Ia	

Patients 2, 3, and 14 were previously reported.<sup>2</sup>

\* How many SD the patients were shorter than Japanese average heights against sex and age (1995).

† HTLV titer was determined by the particle agglutination method (Fujirevio Inc., Tokyo, Japan). Normal range of serum is less than 16-fold and CSF is less than fourfold.

HS-PTH = hypersensitive PTH, assayed with HS-PTH determination kit (YAMASA, Japan); E-H = Ellsworth–Howard; WAIS = Wechsler Adult Intelligence Scale; RBC = red blood cell; ND = not determined; PPHP = pseudopseudohypoparathyroidism; PHP = pseudohypoparathyroidism.

height 153 cm [–0.6 × SD], juvenile-onset HAM/TSP) of Patient 5 (table 1).

The mRNA expression of Gsα was reduced in Patient 3 and her mother, Patient 4, Patient 7 and his mother, and Patient 13, compared with that in normal controls (table 1). Only a few patients were examined because of the large blood volume collection necessary for mRNA preparation.

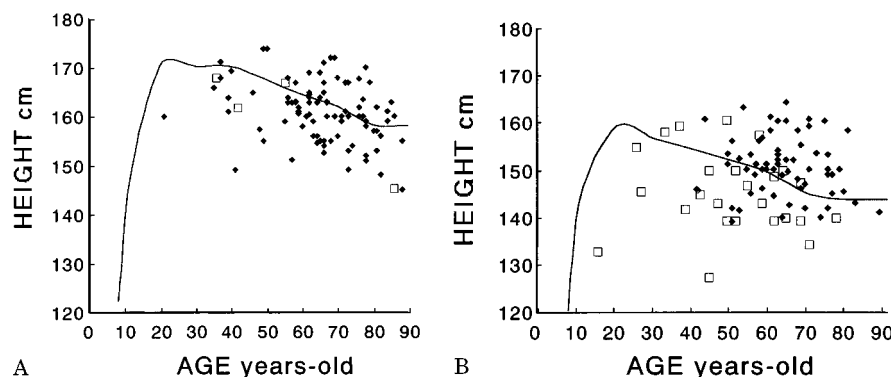
These findings indicate that eight patients possibly had PHP Ia and four patients possibly had pseudopseudohypoparathyroidism (PPHP).

**Discussion.** PHP is a metabolic disorder characterized by AHO and resistance to PTH. PHP Ia and PPHP are genetically the same disease. The decreased activity and the low protein levels of Gsα are responsible for PHP Ia.<sup>4</sup> We diagnosed four patients

with PPHP who had no hormone resistance despite a Gsα deficiency.

Although PHP is clinically diagnosed by the E-H test, we used the E-H test for several patients because the current patients had urinary disturbances. Furthermore, most patients with a normal serum calcium level had normal reactions to PTH in the E-H test.<sup>5</sup> We have no method to diagnose PHP Ib (PTH receptor abnormality), PHP Ic (adenylate cyclase deficiency), and PHP type II. Therefore, we only diagnosed PHP Ia and the variant-type PPHP in the patients with HAM/TSP.

Autosomal dominant transmission is a known inheritance pattern of PHP Ia.<sup>4</sup> Among the families of 12 patients diagnosed with PHP Ia or PPHP, two of their



*Figure. The relation of the heights to the age of male (A) and female (B) juvenile-onset patients with human T-lymphotrophic virus type I-associated myelopathy/tropical spastic paraparesis (HAM/TSP). Many juvenile-onset patients were apparently recognized with short stature compared with adult-onset patients and standard Japanese individuals. Japanese average heights against age and sex (1995) are shown by solid lines. Solid diamonds, adult-onset patients with HAM/TSP; open squares, juvenile-onset patients with HAM/TSP.*

**Table 2** Correlation of patients with juvenile-onset human T-lymphotrophic virus type 1-(HTLV-1-) associated myelopathy/tropical spastic paraparesis to short stature

Stature	Adult onset	Juvenile onset
Normal	231	12
Short <-1 SD*	34	17†
Short <-2 SD*	13	8†

\* Short stature <-1 SD and <-2 SD indicates the patient numbers of the  $-1 \times$  SD and  $-2 \times$  SD shorter than the Japanese standard height. Number of short stature <-1 SD included that of short stature <-2 SD.

†  $p < 0.005$  by  $\chi^2$ .

mothers had PHP Ia or PPHP. The mother of Patient 14 was possibly diagnosed with PPHP because of slightly shorter stature (aged 71 years, height 145 cm [ $-0.6 \times$  SD]), WAIS IQ score of 85, and hypocalcemia (serum calcium level, 8.6 mg/dL).<sup>2</sup> The current findings suggest that these three patients inherited the PHP gene from their mothers and that HTLV-I had been originally transmitted to their mothers by their fathers. Many of the patients' siblings had slightly shorter stature, and most of the current patients were the younger children in their families. However, further investigation was impeded by the death of the other patients' parents.

The annual period prevalence of PHP was 3.4 per million people in 1997 in Japan. Variable clinical severity possibly calculates the number of patients with PHP less than the true number. Results of the current examination suggest that PHP is possibly not a rare disease; however, the incidence of PHP in HAM/TSP appeared high.

Abnormality of PHP is caused in part by reducing 1,25-dihydroxyvitamin D<sub>3</sub> (1,25-(OH)<sub>2</sub>D<sub>3</sub>). 1,25-(OH)<sub>2</sub>D<sub>3</sub> is recognized not only as a calcium regulator but also as an immunoregulatory hormone.<sup>6</sup> Vitamin D deficiency is often accompanied by infections such as tuberculosis.<sup>7,8</sup> 1,25-(OH)<sub>2</sub>D<sub>3</sub> has an inhibitory effect on the release of interleukin-2 (IL-2) and interferon- $\gamma$  from peripheral blood mononuclear cells.<sup>6</sup> Levels of IL-2 mRNA of peripheral blood mononuclear cells from HAM/TSP patients are significantly increased compared with those from asymptomatic HTLV-I carriers and patients with ATL.<sup>9</sup> IL-2 activates polyclonal proliferations of HTLV-I-infected T cells.

1,25-(OH)<sub>2</sub>D<sub>3</sub> inhibited the proliferation of MT-2 cells and the HTLV-I infected T-cell line in a time- and dose-dependent manner.<sup>10</sup> These findings suggest that patients with PHP had an inappropriate immune defense system caused by decreased 1,25-(OH)<sub>2</sub>D<sub>3</sub>, which might be a host factor required for development of HAM/TSP.

Many kinds of diseases have been described in relation to HAM/TSP, such as T-lymphocyte alveolitis, Sjögren syndrome, arthropathy, uveitis, and PHP. These diseases, except for PHP, were probably caused by infiltrations of HTLV-I-infected T cells to the target organ. In contrast, HTLV-I infection does not induce PHP, but PHP may be a risk factor for the occurrence of HAM/TSP.

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