A Case of HTLV-I-associated Myelopathy with IgA Nephropathy and Pseudohypoparathyroidism Type 1

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We report a case of HAM/TSP presenting with short stature, mental retardation, skin eruptions, uterine and ovarian hypogenesis and nephropathy. Skin erythema was noted since from the age of three years old and spasticity of lower extremities from elementary school age. Serum calcium level showed 4.1 mEq/l. Recombinant human PTH infusion resulted in no response of phosphate excretion. The persistent proteinuria prompted renal needle biopsy, which revealed IgA and C3 deposits in glomerular mesangium. A diagnosis of pseudohypoparathyroidism and IgA nephropathy was entertained. This patient with pseudohypoparathyroidism who has a deficient immune system was seized with the early onset of HAM/TSP and IgA nephropathy.

Key words: HAM/TSP, Short stature, Growth hormone, Mental retardation

Recent reports have shown the association of HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP) and various conditions such as broncho-pulmonary disturbance (1), arthritis (2), Sjögren’s syndrome (3) and polymyositis (4, 5). We report a very early clinical onset of a case with HAM having a nephropathy in addition to hypocalcemia, short stature, mental retardation and hypogenesis of uterus and ovaries, for which pseudohypoparathyroidism (PSPH) was entertained. To date, there has been no similar report.

CASE REPORT

A 24-year-old woman was admitted to our hospital in 1976 because of paraparesis observed since her childhood. She was born in 1952 with full-term spontaneous vaginal delivery, weighed 2,630 g, and was exclusively breast fed. By percentile she has had a short stature since she was an infant. Her psychomotor development was slightly delayed. From the age of 3, she has frequently had eczema-like photosensitive exanthema on her face, neck, anterior chest and axillary areas. She could not run fast during her elementary school days. Compared to her brother and sister, her grades were very bad at elementary school. At the age of 9, she had proteinuria and slight generalized edema. Her menarche occurred at 16 yr of age and her menstrual cycle has been irregular. From age 20, she has noted some spasticity of both lower extremities.

Although her parents and siblings were in apparent good health and showed normal stature, she was only 133 cm tall, and weighed 43 kg. Her hair was coarse and dry. Her left fifth metacarpal finger was especially short. The head circumference was 52 cm. The body frame was small and most of her teeth were decayed. Neurologically, her short-term memory was slightly impaired and WAIS I.Q. was 78 (behavioral test, 78; verbal test, 78). She was observed to have a quiet and passive disposition. Her
right and left visual acuity was 20/25 and 20/20, respectively. A perceptive deafness (high tone disturbance) was recognized. The jaw jerk was normal but the other deep tendon reflexes were moderately increased in the upper extremities and prominent in the lower extremities with ankle clonus and Babinski signs. There was urinary incontinence. Gynecologic examination revealed that her uterus was hypogenetic and her ovaries were small although she had normally developed external genitalia and secondary sexual character.

Atypical leukocytes were not seen in the smears of peripheral blood. Urinalysis revealed no glucose but the protein levels ranged from 0.5–3 g/day. Serum sodium, potassium and chloride concentrations were normal. Serum calcium consistently showed 4.1 and 4.2 mEq/l (normal range, 4.5–5.5), magnesium of 1.9 mg/dl (1.6–2.3) and phosphate of 3.7 mg/dl (2.5–4.5). Urinary excretion of calcium and phosphorus over a 24-h period was 0.01 g and 0.043 g, respectively. Renal tubular reabsorption of phosphate was 90.1%. Liver function tests were within normal limits and alkaline phosphatase was 8.9 King-Armstrong units (normal, 8–12 U). Blood urea nitrogen was 10.7 mg; serum creatinine, 0.7 mg/dl; and uric acid, 7.8 mg/dl. Serum protein was 8.2 g/dl and albumin $\alpha_1$, $\alpha_2$, $\beta$, $\gamma$-globulin were 43.4, 3.2, 9.3, 12.8, 31.0%, respectively. Level of IgG was 2,960 mg/dl (800–1,800); IgA, 897 mg/dl (90–450); IgM, 310 mg/dl (60–250) and IgE, 530 mg/dl (45–530).

These elevated levels of immunoglobulins were not monoclonal. Serum complement levels of C3 and C4 were 58.0 mg/dl (55–120) and 40.3 mg/dl (20–50), respectively. Immune complex was not detected by the C4q deviation assay procedure (6) or by the Raji cell binding procedure (7, 8). Bone marrow aspiration showed a total cell count of $146 \times 10^9/\mu l$ including atypical lymphocytes 0.2% and a slightly increased number of plasma cells.

Endocrine examination revealed that thyroid function tests were within normal limits. Serum parathyroid hormone (PTH) was 425.9 pg/ml (180–560) by intermediate portion assay and 0.4 ng/ml (less than 0.5) by C-terminal assay; serum calcitonin was less than 25 pg/ml (less than 165); osteocalcin was 13 ng/ml (2.5–8.5). The recombinant human PTH fragment 1–34 (100 U) (Toyo Jozo Co. Ltd., Shizuoka, Japan) infusion revealed that the urinary phosphate excretion level increased by only 1.5 mg, 2 h after infusion. Renal tubular reabsorption of phosphate was 90.6%. The urinary cyclic AMP excretion level increased to only 0.85 $\mu$ mole in the first hour compared to 0.086 $\mu$ mole each hour before the infusion, suggesting a diagnosis of PSHP type 1. The serum levels of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D (1,25 (OH)$_2$D) were 8.6 ng/ml (9.0–33.9) and 16.5 pg/ml (20–60), respectively. Twenty-four hour urinary excretion levels of 17-hydroxycorticosteroid and 17-ketosteroid were within normal limits. Serum somatomedin C was low (0.58 U/ml; average ± S.D., 0.98 ± 0.34). The basal levels and levels after pituitary releasing hormone infusion are shown in Table 1. In these examinations the release of

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**Fig. 1.** PAS staining of needle biopsied kidney tissue. Glomerular basal membrane was shown to be thick, abundant lymphocyte infiltration was found in the interstitium and some distal convoluted tubules were obstructed and destroyed.

**Fig. 2.** Immunofluorescent staining of the kidney. IgA deposits in the mesangium are notable (707×).
Table 1. Endocrinological Examination

<table>
<thead>
<tr>
<th>Infusion</th>
<th>Determination</th>
<th>0</th>
<th>15</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120min</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH-RH (100 µg) LH(mIU/ml)</td>
<td>51.1 (9-33)*</td>
<td>124</td>
<td>170</td>
<td>175</td>
<td>176</td>
<td>188</td>
<td></td>
</tr>
<tr>
<td>FSH(mIU/ml)</td>
<td>17.4 (5-19)</td>
<td>24.9</td>
<td>32.1</td>
<td>34.3</td>
<td>39.0</td>
<td>40.5</td>
<td></td>
</tr>
<tr>
<td>Insulin (0.1 U/kg) GH(ng/ml)</td>
<td>5.7 (less than 5)</td>
<td>74</td>
<td>10.0</td>
<td>47</td>
<td>18.9</td>
<td>15.0</td>
<td>149</td>
</tr>
<tr>
<td>Glucose(mg/dl)</td>
<td>91</td>
<td>47</td>
<td>181</td>
<td>172</td>
<td>149</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRH (0.5 mg) GH(ng/ml)</td>
<td>5.8 (no reaction)</td>
<td>22.5</td>
<td>18.9</td>
<td>16.6</td>
<td>15.2</td>
<td>12.4</td>
<td></td>
</tr>
<tr>
<td>TSH(uU/ml)</td>
<td>4.5 (less than 10)</td>
<td>16.7</td>
<td>16.6</td>
<td>15.2</td>
<td>12.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRL(ng/ml)</td>
<td>51.2 (3-20)</td>
<td>95.3</td>
<td>80.6</td>
<td>68.7</td>
<td>56.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose (100 g)</td>
<td>Glucose(mg/ml)</td>
<td>107</td>
<td>185</td>
<td>181</td>
<td>149</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin (µ/ml)</td>
<td>16.5</td>
<td>222</td>
<td>172</td>
<td>149</td>
<td></td>
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</table>

Serum levels of each hormone and glucose were determined at the indicated time after the infusion of the glucose per os or stimulating hormone (intravenously).

*Numbers in parenthesis indicate the normal range.

Luteinizing hormone (LH), follicle stimulating hormone (FSH), human growth hormone (HGH) and prolactin (PRL) were prominently increased in the follicular phase.

Cerebrospinal fluid examination showed cells of 20/3 per µl, all of which were lymphocytes. The concentrations of protein and glucose were within normal limits. Her HTLV-1 virus titer (particle aggregation method) was 2,048 x (less than 128 x ) in serum and 252 x (less than 16 x ) in cerebrospinal fluid.

Electroencephalogram showed that the basic rhythm was poorly organized, diffuse 8-9 Hz activity which was spiky. Brain CT showed some bilateral calcifications in the basal ganglia and slight brain atrophy. There were no pituitary tumors by MRI.

Drip infusion pyelogram showed slight atrophy of the kidneys bilaterally and the renal pelvices and calyces were not dilated. PSP excretion rate was 74.1% after 120 min. The specific gravity of the early morning first urine was 1.025 using the Fishberg concentration test. The renal plasma flow (C_{PAH}) was 1,150 ml/min and glomerular filtration rate (C_{in}), 184 ml/min.

Her paraparesis gradually worsened and she became wheelchair-bound in 1980. In the same year a series of generalized tonic-clonic seizures occurred, sometimes associated with hallucinations and illusions. After the administration of 1-hydroxyvitamin D (0.5 µg/day) was begun in 1986, the serum calcium level normalized to 4.5 mEq/l, and EEG improved (emerging of the organized 8-9 Hz activity and disappearance of the spiky activity). She has had complete menopause since the age of 37.

Urinary incontinence and frequency due to neurogenic bladder slowly progressed in severity and proteinuria persisted. In 1988, creatinine clearance...
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was 50.9 l/day and serum creatinine and BUN levels were 1.2 mg/dl and 24.9 mg/dl, respectively. PSP excretion rate was 45.5% after 120 min and the specific gravity of early morning urine was 1.012.

A renal biopsy revealed thick glomerular basal membranes, and IgA and IgG deposition in the mesangium. Complement C4d and C3 were also noted in the mesangial areas by means of immunofluorescent staining. However, monoclonal antibody of P24, HTLV-1 surface protein, was not detected in this biopsy specimen. There was obstruction of the distal convoluted tubules, destroyed glomeruli, and a large quantity of interstitial lymphocyte infiltration. The arteriolar wall was thick and there was no IgA deposition (Figs. 1 and 2).

DISCUSSION

The patient presented typical HAM/TSP, IgA nephropathy and PSHP. Although she had a short stature which is a characteristic sign of PSHP, HGH was strongly released by the injection of insulin and even TRH. In normal individuals, TRH injection does not induce such a paradoxical release of HGH. This indicates an abnormal sensitivity of the receptor of HGH releasing cells in the pituitary gland.

However, when the serum calcium level became 4.5 mEq/l from 4.1 mEq/l, the response to the injected TRH was slight but still present (2.3 ng/ml before the injection and 6.5 ng/ml at 90 min). Furthermore, although she had a hypogenetic uterus and ovaries, LH-RH infusion showed that LH and PRL release were high. These abnormal endocrine responses can be found in patients with PSHP type 1 (9–14). The low response of the HGH release to hypoglycemia has been previously shown (10, 12, 14) although high responses are also found (9, 11, 13). The HGH reaction to TRH in the present case in which the absence of pituitary tumor is confirmed is very rare.

Vitamin D deficiency rickets is often accompanied by infections and fungal infections (candidiasis) which sometimes complicate hypoparathyroidism (15). The immune deficiency in these diseases is believed to be due to the decreased level of 1,25(OH)₂D₃, which had an effect in the regulation of the immune response (16). 1,25(OH)₂D₃ inhibits the proliferation of macrophages and promotes the immune response to antigen (17–20). The signs and symptoms of HAM/TSP starting very early in childhood of the patients with PSHP is possibly involved in the insufficiency of the immune defense system due to the decreased 1,25(OH)₂D₃ level, although the mere coincidence can not be denied. The detection of integrated HTLV-1 proviral DNA into lymphocyte DNA revealed that the estimated amount was higher in HAM/TSP patients than in asymptomatic HTLV-1 carriers. In a HAM patient, HTLV-1 infection progressed to a much greater extent than in asymptomatic carriers (21). Skin erythema, which is a characteristic sign of HTLV-1 infection, is a manifestation of the infiltration of infected and activated lymphocytes. The present patient suffered from erythema from the age of three, indicating a very early infection. The nephropathy in the case was considered to be induced by long persistent infection of HTLV-1, as many reports have discussed nephropathy in children with acquired immunodeficiency syndrome (22) as well as in mice and dogs with retrovirus infection.

It has been presumed that the fatal SLE-like glomerulonephritis which naturally develops in the New Zealand mouse is associated with retroviruses (23–25). The glycoprotein (GP 70) of murine leukemia virus (retrovirus) was found to be deposited in the subepithelium of the glomerulus (26, 27). Furthermore, cats usually die because of the natural onset of lymphoma associated glomerulonephritis, caused by feline leukemia virus (retrovirus) (28). There is a report of 2 cases with nephrotic syndrome which were also associated with chronic lymphocytic leukemia (29). The deposition of HTLV-1 antigen was found in the real glomerulus of an adult T cell leukemia patient (30). It has been reported that patients with acquired immunodeficiency syndrome have also been complicated with nephropathy (22, 31). The biopsy findings of the kidney in this case were compatible with IgA nephropathy (32) with C3 and C4q deposition, however, the P24 of the HTLV-1 viral component was not found by immunofluorescent staining. IgA nephropathy is known to be associated with several diseases such as B-type hepatitis virus infection (33, 34), and respiratory diseases (35–37). Persistent high levels of serum IgA were seen in more than half of HAM patients and this IgA was polyclonal. Serum polyclonal IgA is usually increased in respiratory diseases and some HAM patients have respiratory...
signs and symptoms such as dyspnea, and productive cough. They were thought to be suffering from a bronchopulmonary disease (1). However, the present patient did not have a respiratory disease but did have a persistent high IgA level. Although IgA was deposited in the mesangium, the detailed mechanism is still uncertain and immune complex was not detected in her serum. In the case of SLE-like glomerulonephritis in the New Zealand mouse, GP 70 appears first in the serum and is secondarily deposited in the glomerulus (38). Serum GP 70 levels are correlated with the severity of the glomerulonephritis (39). Therefore, the mechanism of deposition is different between the mouse and the present case.

HAM has been associated with arthritis (2) and Sjögren disease (3) as well as bronchopulmonary diseases (1). T-lymphocyte (CD 4 and 8) infiltration was found in these organs. There was a large quantity of lymphocyte infiltration in the interstitium of the kidney biopsy specimen from the present case. Some distal convoluted tubules were obstructed. The findings of the lymphocyte infiltration and the obstruction of renal tubule can also be found in the kidneys of cases with pyleonphritis, which is frequently a complication of neurogenic bladder. Although we could not definitively show that lymphocyte infiltration was due to the HTLV-1 infection, this infiltration is a characteristic finding in HTLV-1 infection.

In conclusion, we report probably the first case in which HTLV-1 associated myelopathy/tropical spastic paraparesis, IgA nephropathy and pseudohyoparathyroidism were associated.

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