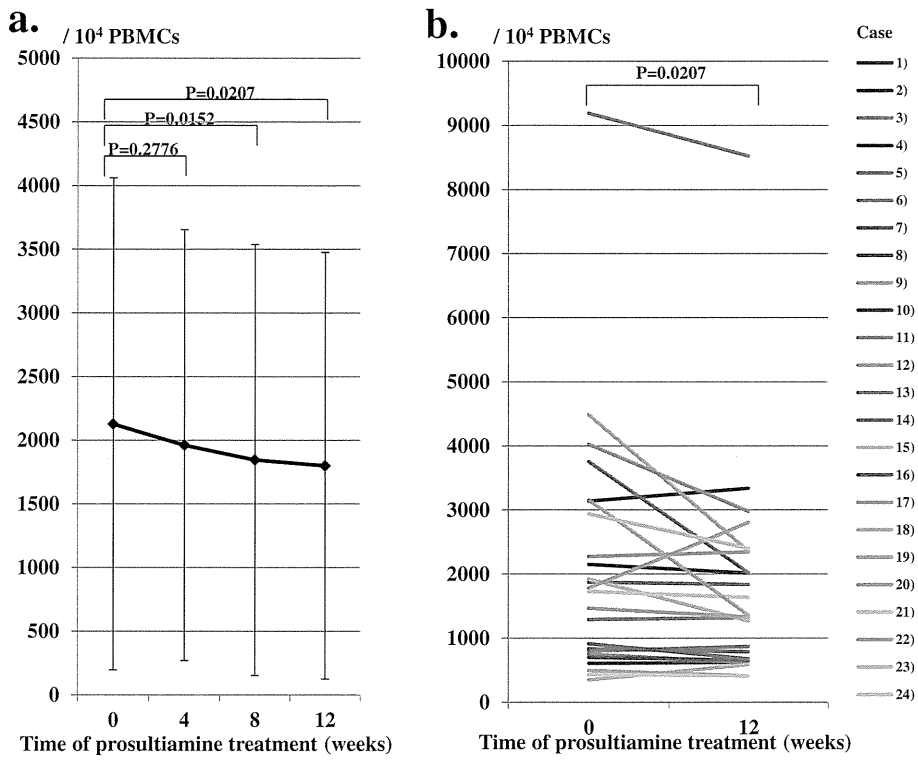

Figure 2 Change in human T lymphotropic virus type I (HTLV-I) proviral copy numbers in peripheral blood mononuclear cells (PBMCs). (a) HTLV-I proviral copy numbers from 10^4 PBMCs decreased gradually until 12 weeks after prosultiamine treatment. The level of HTLV-I proviral copy numbers 12 weeks after prosultiamine treatment decreased by 15.4% compared with the time at pretreatment. **(b)** Changes in HTLV-I proviral copy numbers in each case between pretreatment and 12 weeks after prosultiamine treatment. Statistical significance was determined by the Wilcoxon signed-rank test.

of approximately 30% to 50% in HTLV-I proviral copy numbers was observed in cased 8, 9, 11, 15 and 22.

Adverse effects

There were no serious adverse effects except mild epigastric discomfort rated as '2' evaluated according to the Global Overall Symptom scale [18] in three HAM/TSP patients. This symptom immediately resolved after this clinical trial.

Discussion

Effective therapeutic regimens are needed urgently to treat such myelopathic symptoms of HAM/TSP as spasticity of lower extremities and urinary disturbance. To this end, we administered prosultiamine *via* the oral route for 12 weeks in subjects with HAM/TSP. This treatment improved (i) the motor ability of the lower extremities by decreasing spasticity, and (ii) urinary function. The mean duration of illness of the patients enrolled in this study was relatively long (approximately 21 years), so the efficacy of this treatment is promising. Indeed, these data suggest that the pathological processes in the spinal cord of HAM/TSP patients are partially reversible and treatable even if the tissues are damaged over a long period of time.

The most striking effect in this clinical trial was the amelioration of urinary disturbance in HAM/TSP patients. The common urodynamic findings in HAM/TSP patients are DO, DSD and detrusor hypoactivity [19]. However, as evaluated by UDS, prosultiamine treatment resulted in a significant increase in detrusor pressure and bladder capacity followed by an increase in maximum flow rate with improved DO. DSD also improved in 45.5% (5 of 11 patients observed at pretreatment) (P = 0.0736). Although this value did not reach statistical significance, it showed a tendency of improvement. This is the first time that the therapeutic effect for urinary dysfunction in HAM/TSP patients was evaluated in detail by UDS. With respect to the effect of urinary conditions on the QoL of HAM/TSP patients, nocturia, urgency, increased frequency of urination and dysuria have been reported to be the main problems [20]. Therefore, we evaluated the change in QoL of patients using N-QoL questionnaires during treatment. The improved UDS corresponded with improvements in the score of N-QoL questionnaires. Concomitant pharmacological therapies for the neurogenic bladder were continued during the present study. However, the efficacy of prosultiamine treatment, even in patients who were not having concomitant therapies (cases 5, 6,

11, 13, 23, and 24), strongly suggested that urological improvement was dependent solely upon prosultiamine treatment (Table 1). Overall, these data suggest that prosultiamine treatment can reverse bladder dysfunction in HAM/TSP patients.

Recently, two reports have focused on targeting HTLV-I in therapeutic trials against HAM/TSP. One study used reverse transcriptase (RT) inhibitors, whereas the other used a histone deacetylase enzyme inhibitor for treatment [21,22]. In the former, the results of combination therapy (zidovudine + lamivudine) in a randomized, double-blind, placebo-controlled study suggested that RT inhibitors were not effective for targeting HTLV-I for the treatment of HAM/TSP. In the latter study, long-term treatment using valproic acid did not reduce the number of HTLV-I -infected cells in peripheral blood [22]. A decrease in the HTLV-I provirus in PBMCs was one of the primary endpoints in our recent report [11]. Indeed, oral administration of prosultiamine induced a significant decrease in HTLV-I proviral copy numbers in PBMCs, However, the rate of reduction was not as high as we had expected. This finding might suggest a limitation of the protocol used in the present study. Thus, the remarkable improvement of motor dysfunction and urinary function in the present study cannot be attributed solely to a decrease in HTLV-I proviral copy numbers in PBMCs. The exact mechanism is not known. Prosultiamine was originally developed for efficient access of vitamin B1 to nervous tissues [10]. Although this drug is reduced to a part thiamine and propyl disulfide by the intracellular reducing system after penetration to the cells [10], it is suspected that the disruption of intracellular redox system is induced during reduction of disulfide bond leading to the apoptosis of HTLV-I-infected cells [11]. Therefore, it might be conceivable that, as one of the mechanisms, this drug functions to induce the apoptosis of HTLV-I-infected cells in the spinal cord even if the extent of reduction of the number of HTLV-I-infected cells in PBMCs is relatively small. Further investigations including analysis of cerebrospinal fluid are needed to elucidate the exact mechanism of action of prosultiamine.

Conclusions

In the present work we have demonstrated that oral administration of prosultiamine can safely promote improvement of motor function of the lower extremities based on a reduction of spasticity along with appreciable amelioration of urinary disturbance associated with a decrease in the amount of HTLV-I provirus in peripheral blood. Our results suggest that prosultiamine could be a promising therapeutic tool for HAM/TSP patients. Therefore, further studies are warranted, such as the evaluation of prosultiamine treatment against HAM/TSP in a large-scale, randomized, controlled study.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
TN designed the study, assessed the neurological findings, analyzed data, and wrote the paper. TMatsuo designed the study, analyzed data, and contributed to the urological studies. HSakai contributed to the urological studies. TF and TN-M assessed the neurological findings. TN, TF and SY managed the blood supply and laboratory studies. KY and HSasaki handled the prosultiamine and enclosed it in capsules. IK, TMatsuzaki, YN, KN, HN, KS, and AK were involved in managing the patients. All authors contributed to the manuscript and approved the final version of the report.

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NEW DEVELOPMENTS FROM ASIA

Prosultiamine treatment as a new therapeutic strategy in human T lymphotropic virus type I-associated myelopathy/tropical spastic paraparesis

Human T lymphotropic virus type I (HTLV-I)-associated myelopathy/tropical spastic paraparesis (HAM/TSP) is a chronic myelopathy characterized by motor dysfunction of the lower extremities and urinary disturbance.[1] The primary neuropathological feature of HAM/TSP is chronic inflammation in the spinal cord caused by high HTLV-I proviral load in peripheral blood mononuclear cells (PBMC). Therefore, immunomodulatory therapy, such as corticosteroid hormones and interferon-α, has been the main treatment for HAM/TSP patients.[2] However, there are many issues in long-term treatment with these drugs, such as insufficient effects and various side-effects. Once the myelopathy develops, the main neurological symptoms, such as motor dysfunction of the lower extremities accompanied by urinary disturbance, are progressive and lead to a deterioration in the quality of life of patients. Therefore, novel and safe therapeutic regimens are urgently required for HAM/TSP patients to use as a treatment, or prevent disease progression.

Prosultiamine (Alinamin), a vitamin B_1 derivative, is safely available in Japan for the treatment of Wernicke's encephalopathy and polyneuropathy induced by deficiency of vitamin B_1. Based on the data that prosultiamine can induce the caspase-dependent apoptosis of HTLV-I-infected cells through disruption of intracellular redox reactions by a disulfide moiety in its structure,[3] we carried out a clinical trial with prosultiamine for 24 HAM/TSP patients using an open-labeled design. Here, I will show the remarkable efficacy of prosultiamine treatment against HAM/TSP patients without serious adverse effects.[4,5]

Prosultiamine 300 mg was given orally once daily for 12 weeks. As a result, improvement in the motor function of the lower extremities based on a reduction in spasticity (e.g. decrease in time required for walking and descending a flight of stairs) was observed. Interestingly, this treatment induced the striking amelioration of urinary disturbance. In an urodynamic study (UDS), bladder capacity and detrusor pressure, and then maximum flow rate, increased significantly. Detrusor overactivity and detrusor-sphincter dyssynergia improved in 68.8% and 45.5% of patients, respectively. Improvement in UDS corresponded with improvements in the score of nocturia quality of life questionnaire. Thus, given that the mean duration of illness of the patients enrolled in the present study was relatively long (approximately 21 years), the efficacy of this treatment is promising.

In the present study, HTLV-I proviral copy numbers in PBMC decreased significantly (approximately 15.4%) compared with pretreatment levels. However, the remarkable clinical improvement in the present study cannot be attributed solely to a decrease in HTLV-I proviral copy numbers in PBMC. Although the exact mechanism is not known, it might be conceivable that, as one of the mechanisms, prosultiamine functions to induce the apoptosis of HTLV-I-infected cells by the disruption of intracellular redox system in the spinal cord, even if the extent of reduction of the number of HTLV-I-infected cells in PBMC is relatively small. Further investigations including analysis of cerebrospinal fluid are required to elucidate the exact mechanism of action of prosultiamine.

Overall, the present results suggest that prosultiamine could be a new promising therapeutic tool for HAM/TSP patients. Therefore, further studies are warranted for the evaluation of prosultiamine treatment against HAM/TSP in a large-scale, randomized, controlled study and long-term treatment.

Competing interests

None.

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ORIGINAL ARTICLE

HTLV-I virological and histopathological analysis in two cases of anti-centromere-antibody-seropositive Sjögren's syndrome

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Abstract
Introduction The aim of this study was to show the clinical and pathological characteristics of anti-centromere-antibody (ACA)-seropositive Sjögren's syndrome (SS) in two anti-human T-cell leukemia virus type I (HTLV-I)-seropositive patients.
Methods One patient was an HTLV-I carrier whereas the other was diagnosed with HTLV-I-associated myelopathy (HAM). Background data including serum HTLV-I titers, viral loads, and cytokine profiles were recorded. Azocarmine with aniline blue (Azan)–Mallory staining and immunohistochemistry of the labial salivary glands (LSGs) and a muscle biopsy specimen from the HAM patient were performed.
Results Serum transforming growth factor beta (TGF-β), tumor necrosis factor alpha (TNF-α), and HTLV-I viral load were high in the HAM-SS patient compared with the HTLV-I carrier. Fibrous change in LSG was prominent in the HAM-SS patient. Although TGF-β expression was similar in the two patients, expression of HTLV-I-related proteins including p12, p28, group-specific antigen (GAG), and nuclear factor kappa-B (NF-κB) in the LSG were dominantly detected in the HAM-SS patient. Frequency of TGF-β staining in HTLV-I-seropositive SS patients without ACA, HTLV-I-seronegative SS patients with ACA, and HTLV-I-seronegative SS patients without ACA was lower than that of the previous two patients.
Conclusion A high HTLV-I viral load in situ is supposed to promote the production of cytokines, especially TGF-β, resulting in the fibrous change of LSG in ACA-seropositive SS patients.

Keywords HTLV-I infection · Anti-centromere antibody · Sjögren's syndrome · Cytokine

Abbreviations

ACA	Anti-centromere antibody
ANA	Anti-nuclear antibody
CSF	Cerebrospinal fluid
HAM	HTLV-I-associated myelopathy
HTLV-I	Human T-cell leukemia virus type I
IFN-γ	Interferon gamma
MNC	Mononuclear cell
LSG	Labial salivary gland
SS	Sjögren's syndrome
TGF-β	Transforming growth factor beta
TNF-α	Tumor necrosis factor alpha

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Introduction

Human T-cell leukemia virus type I (HTLV-I) is known to be one of the causative agents of Sjögren's syndrome (SS) [1, 2]. Our previous epidemiologic studies show a close association between HTLV-I and SS [3, 4]. In addition, we found a significantly high prevalence of SS in patients with HTLV-I-associated myelopathy (HAM) [3, 5]. On the other hand, anti-centromere antibody (ACA) is known as a second class of autoantibodies in SS patients [6, 7]. Our previous report revealed that ACA is detected in only 4 % of HTLV-I-seropositive SS cases, demonstrating that HTLV-I might not be involved in the pathogenesis in ACA-seropositive SS patients [8]. However, if HTLV-I infection coincidently occurs in ACA-seropositive SS patients, the influence of ACA on HTLV-I-associated SS might become obvious. In this study, we report two cases of ACA-seropositive SS patients who were also seropositive for anti-HTLV-I antibody. One patient was complicated with HAM, whereas the other was an HTLV-I carrier. The variation in HTLV-I viral road in these patients appears to explain the differences in labial salivary gland (LSG) histopathology and cytokine profile.

Patients and methods

Patients

Case 1

This was a 61-year-old female patient who complained of sicca symptoms. Both ACA and anti-HTLV-I antibody measured by chemiluminescent enzyme immunoassay (CLEIA) were highly positive, as shown in Table 1. As no other symptoms or signs, including in the neuromuscular systems, were found in this patient, she was classified as an HTLV-I carrier.

Case 2

A 57-year-old female patient who complained of sicca symptoms and myalgia was diagnosed with HAM based on the diagnostic guidance for HAM determined by the Ministry of Health, Labour and Welfare. She had slowly progressive and symmetrical pyramidal tract damage with positive anti-HTLV-I antibody in both serum and cerebrospinal fluid (CSF). Antibodies against gp46, p53, p24, and p19 of HTLV-I in CSF were all positive. Serum ACA was also positive at a high titer (Table 1). She also suffered from inflammatory myopathy as evidenced by the elevation of muscle enzymes and by magnetic resonance imaging and muscle biopsy findings.

Both patients were diagnosed with SS according to the revised criteria [9], as proposed by the American–European Consensus Group. In both cases, HTLV-I viral roads in sera and serum cytokines including tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), and transforming growth factor beta (TGF-β) were measured. For comparison, we studied the three groups of patients: (1) HTLV-I-seropositive SS patients without ACA, (2) HTLV-I-seronegative SS patients with ACA, and (3) HTLV-I-seronegative SS patients without ACA with respect to TGF-β immunostaining of LSG (four patients each in three groups).

LSG biopsy

LSG biopsy from the lower lip was performed under local anesthesia in SS patients. Informed consent to use biopsy samples was obtained from all participating patients at the commencement of the study. The study was conducted with the approval of the human ethical committee of our institution. The classifications of Chisholm and Mason [10] were used to determine the severity of mononuclear cell (MNC) infiltration.

Azan–Mallory staining and immunohistochemistry of labial salivary glands

Formalin-fixed, paraffin-embedded sections (3-μm thick) from the LSGs of these ACA-seropositive SS patients were used for azocarmine with aniline blue (Azan)–Mallory staining and immunohistochemistry. The sections were then stained using the Histofine Simple Stain Kit (Nichirei Co., Tokyo, Japan) with mouse anti-human CD4, CD8, CD20, and CD68 antibodies (DakoCytomation, Glostrup, Denmark), mouse anti-HTLV-I [p19, p28, and group-specific antigen (GAG)] antibody (Chemicon International Inc., Temecula, CA, USA), mouse anti-nuclear factor kappa B (NF-κB) p65 antibody (Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA), and mouse anti-TGF-β antibody (LifeSpan BioSciences, Inc., Seattle, WA, USA). Briefly, endogenous peroxidase was inactivated in a 3 % hydrogen peroxide (H_2O_2) solution after microwave epitope retrieval. These sections were then blocked with 5 % normal horse serum, followed by incubation with monoclonal and polyclonal antibodies in a humid chamber for 60 min at room temperature. After incubation, all sections, including the negative control sections, were treated with peroxidase-conjugated secondary antibodies for 30 min. The color was developed by soaking the sections in 3.3′-diaminobenzidine (DAB) and H_2O_2 for 10 min, followed by counterstaining by soaking the sections in hematoxylin solution. Negative

Table 1 Background information and serum data of the human T-cell leukemia virus type I (HTLV-I)-associated anti-centromere antibody (ACA)-seropositive patients

	Case 1 HTLV-I carrier with ACA-seropositive SS	Case 2 HAM with ACA-seropositive SS
Age and gender	61 years old, female	57 years old, female
Xerostomia	Positive	Positive
Xerophthalmia	Positive	Negative
Schirmer test (right/left mm; <5 mm: positive)	5/4	11/11
Saxon test (g/2 min; <2 g: positive)	1.47	2.7
ANA: pattern	160×, centromere	640×, centromere
Anti-SS-A antibody: normal 10–30 U/ml	0.7	0.9
Anti-SS-B antibody: normal 15–25 U/ml	0.9	0.5
ACA: normal <16 index	172.8	165.0
IgG: normal 870–1,700 mg/dl	1,712	1,623
Rheumatoid factor: normal <15 IU/ml	11.4	17.0
Sialography[a] (Rubin and Holt)	Stage 1	Stage 2
Lip biopsy grade[b] (Chisholm and Mason)	3	3
LST (cpm)	105,936/617	184,859/19,319
PHA(+)/no stimulation		
LST (cpm)	160,934/617	102,299/19,319
ConA(+)/no stimulation		
Serum anti-HTLV-I antibody: normal <1.0 COI	>45	>45
Serum viral load (copies/10^4 cells)	<53	373
Serum TNF-α: normal 0.6–2.8 pg/ml	1.0	2.9
Serum IFN-γ: normal <0.1 IU/ml	<0.1	<0.1
Serum TGF-β: normal 1.56–3.24 ng/ml	2.76	12.6

Anti-SS-A Ab and anti-SS-B Ab (Mesacup SS-A/Ro test and SS-B/La test; Medical and Biological Laboratories, Nagoya, Japan) and ACA (Mesacup-2 test CENP-B; Medical and Biological Laboratories, Nagoya, Japan) were measured using an enzyme-linked immunosorbent assay (ELISA) kit. Serum anti-HTLV-I antibody was measured by chemiluminescent enzyme immunoassay, and HTLV-I viral load was measured by the FastStart DNA Master Hybridization probe method. Serum TNF-α and TGF-β were measured by ELISA. Serum IFN-γ was measured by enzyme immunoassay. Data shown represent the period before treatments with agents such as glucocorticoids or immunosuppressive agents

SS Sjögren's syndrome, *ANA* anti-nuclear antibody, *COI* cutoff index, *ConA* concanavalin A, *cpm* count per minute, *HAM* HTLV-I-associated myelopathy, *Ig-G* immunoglobulin G, *LST* lymphocyte stimulation test, *PHA* phytohemagglutinin, *TNF* tumor necrosis factor, *IFN* interferon *TGF* transforming growth factor

[a] Sialography grading was determined by Rubin and Holt. Stages 1 and 2 represent punctate and globular patterns, respectively

[b] Grading defined by Chisholm and Mason: the presence of at least one focus of mononuclear cells per 4 mm^2 section = grade 3

control sections were treated with mouse immunoglobulin (Ig)G1.

Results

Clinical and serological data with cytokine profile

As shown in Table 1, a high ACA titer was detected in both patients. Serum IgG was almost normal, which is characteristic in ACA-seropositive SS patients [6]. As patient 2 was diagnosed with HAM, spontaneous proliferation of MNCs was significantly higher than in patient 1. Serum HTLV-I viral load was 373 copies/10^4 cells in patient 2, which is obviously higher than in patient 1 (<53 copies/10^4 cells). Serum TNF-α and TGF-β levels in patient 2 were increased compared with those in patient 1, although serum IFN-γ in both patients was within normal limits.

Azan–Mallory staining and immunohistochemical analysis

MNC infiltration was similar in both patients; however, Azan–Mallory staining showed a stronger fibrosis in patient 2 than in patient 1 (Fig. 1). In patient 2, TGF-β was highly stained in infiltrating MNCs and vessels, except in ductal and acinar cells. TGF-β staining, although weaker than MSG, was also performed in the muscle in patient 2. Accordingly, infiltration of CD4+ lymphocytes, which were dominant compared with CD20 and CD68, was shown in the LSGs of both patients (Fig. 2). Although CD8+ lymphocytes were also scattered in LSGs, CD4+

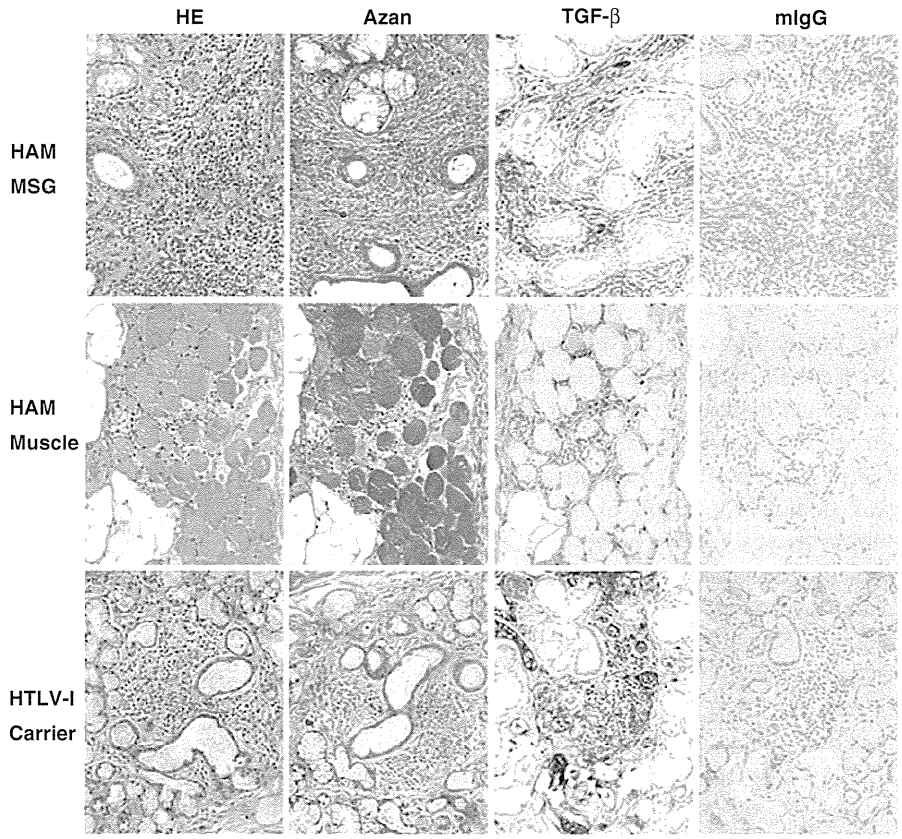

Fig. 1 Azocarmine with aniline blue (Azan)–Mallory staining and transforming growth factor beta (TGF-β) immunostaining in the labial salivary gland (LSG). Azan–Mallory staining and immunohistochemistry after epitope retrieval were performed for formalin-fixed, paraffin-embedded sections (3-μm thick) from the LSG using the Histofine Simple Stain Kit (Nichirei Co., Tokyo, Japan). The primary antibodies used for immunohistochemistry were TGF-β and mouse immunoglobulin (Ig)G1 (×200). Hematoxylin was used as a counterstain

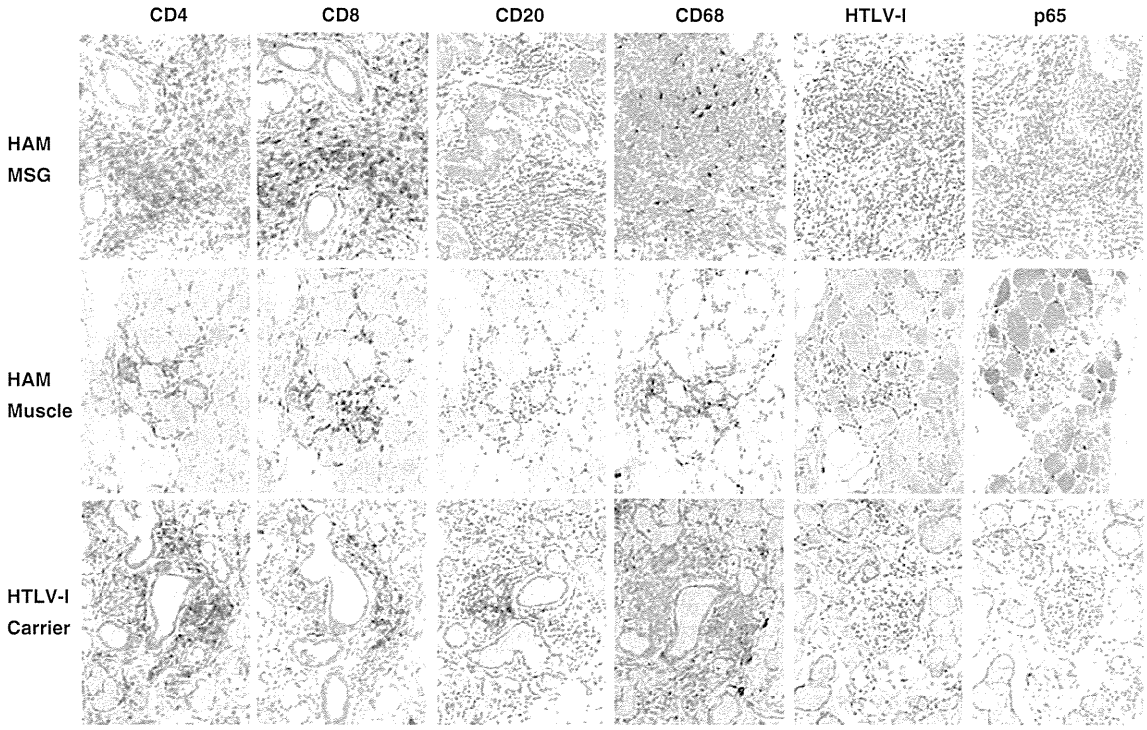

Fig. 2 Immunohistochemistry in the labial salivary gland (LSG). Immunohistochemistry after epitope retrieval was performed for formalin-fixed, paraffin-embedded sections (3-μm thick) from the LSG using the Histofine Simple Stain Kit (Nichirei Co., Tokyo, Japan). The primary antibodies used for immunohistochemistry were CD4, CD8, CD20, nuclear factor kappa B (NF-κB) (p65), and human T-cell leukemia virus type I (HTLV-I) [p19, p28, group-specific antigen (GAG)]. Lymph node from a patient with adult T-cell leukemia was used as a positive control for staining HTLV-I-related proteins (data not shown) (×200). Hematoxylin was used as a counterstain

and CD8+ lymphocytes were found in a muscle specimen from patient 2. It is interesting to note that HTLV-I-related proteins including p19, p28, and GAG were detected in the nuclei of a large percentage of infiltrating MNCs in LSGs and in the muscle specimen in patient 2, which was in accordance with the distribution of NF-κB p65.

TGF-β immunostaining in SS in the presence or absence of anti-HTLV-I antibody or ACA

We finally showed TGF-β immunostaining according to the presence of anti-HTLV-I antibody or ACA (Fig. 3). We performed these experiments in four patients each in three groups and show representative results (Fig. 3). In the HTLV-I-seropositive SS patients without ACA, TGF-β was dominantly found in vascular endothelial cells or fibrous tissues in LSG; however, the frequency of TGF-β+ cells (patients A–D in Fig. 3) appeared to be lower than the patients in cases 1 and 2 in Fig. 1. In the HTLV-I-seronegative SS patients with ACA, TGF-β was seen in infiltrating MNCs, vascular endothelial cells, and fibrous tissues in LSG. Then, in the HTLV-I-seropositive SS patients without ACA, TGF-β expression was similar to HTLV-I-seronegative SS patients with ACA (patients E–H in Fig. 3). In contrast, TGF-β expression was less in HTLV-I-seronegative patients without ACA (patients I, K, L) compared with other groups. In a HTLV-I-seronegative SS patient without ACA (as in patient J), TGF-β was not found in fibrous cells but in MNCs.

Discussion

Both HTLV-I and ACA are known to contribute to SS [1–8]; however, this coincidence of HTLV-I and ACA is supposed to occur with low frequency [8]. Our two cases presented here are rare but may illustrate the in vivo role of HTLV-I in patients with ACA-seropositive SS. Although both patients showed grade 3 MNC infiltration in LSGs, results from exocrine function tests, including Schirmer test and Saxon test in patient 1, were worse than those in patient 2. Except for the degree of MNC infiltration in LSGs, other factors such as aquaporin-5 distribution or type 3 muscarinic receptors [11, 12] might affect lacrimal and salivary secretion. With respect to MNC infiltration into the LSG, both cases showed similar findings. However, there were significant differences in fibrosis determined by Azan–Mallory staining and cytokine profiles.

As patient 2 was diagnosed with HAM, the HTLV-I viral load was high in comparison with patient 1, a finding that is consistent with previous reports [13]. Striking differences were observed in the Azan–Mallory staining findings; however, both patients showed high TGF-β expression in LSGs. TGF-β is a key cytokine for promoting the fibrotic process; thus, the prominent fibrosis of LSG is believed to be driven by TGF-β. Fibrosis was found in the LSG of both patients, which might be explained to some extent by the presence of ACA, as we previously reported [6]. However, a recent report found that HTLV-I basic-leucine zipper (bZIP) factor enhances TGF-β signaling through the p300 coactivator [14]. As strong expression of HTLV-I-related proteins was found in the LSG of patient 2, the TGF-β signaling pathways were suggested to be promoted in situ by HTLV-I, resulting in marked fibrosis. A similar phenomenon might occur in the muscle of patient 2, resulting in inflammatory myopathy. We previously reported that myopathy or uveitis was one characteristic of HTLV-I-seropositive SS patients [15]. With respect to a low level of IFN-γ, Santos et al. [16] demonstrated that administration of exogenous TGF-β induced a decrease of IFN-γ in cells from HTLV-I carriers, suggesting the possibility of the modulation of IFN-γ by TGF-β in HTLV-I-seropositive individuals. The high TNF-α level in patient 2 may also be driven by HTLV-I, as indicated for TGF-β.

To show the involvement of HTLV-I and ACA toward TGF-β expression, we examined TGF-β immunostaining for HTLV-I-seropositive patients without ACA, HTLV-I-seronegative patients with ACA, and HTLV-I-seronegative without ACA (Fig. 3). Although the precise quantitative analysis was not performed in this study, it may demonstrate that TGF-β expression in vascular endothelial cells and fibrous tissues of LSGs is more prominent in SS patients positive for both anti-HTLV-I antibody and ACA (two cases in Fig. 1) compared with SS patients positive for either one alone [two groups (patients A–H in Fig. 3)]. Accordingly, TGF-β expression in the above-mentioned sites was less in SS patients who were not positive for either anti-HTLV-I antibody or ACA (patients I–L in Fig. 3) in comparison with other groups. Therefore, we speculate that the synergistic effect of HTLV-I infection with ACA-carrying status induces the expression of TGF-β in LSGs, especially in vascular endothelial cells and fibrous tissue of SS patients (Fig. 4). However, we also found intense expression of TGF-β in MNCs even in HTLV-I-seronegative patients without ACA. As fibrous change determined by Azan–Mallory staining was not so significant in these patients, TGF-β in MNCs of LSGs may not be directly associated with the fibrotic process. In fact, TGF-β is known to be produced by CD4+ T lymphocytes [17] and influenced by other cytokines, such as IFN-γ [18]. Therefore, the two phenomena—Azan–Mallory-stain-proven fibrosis and TGF-β expression—should be carefully determined in patients with SS. Further studies with a larger number of participants and more definitive qualification approaches are necessary to prove our hypothesis.

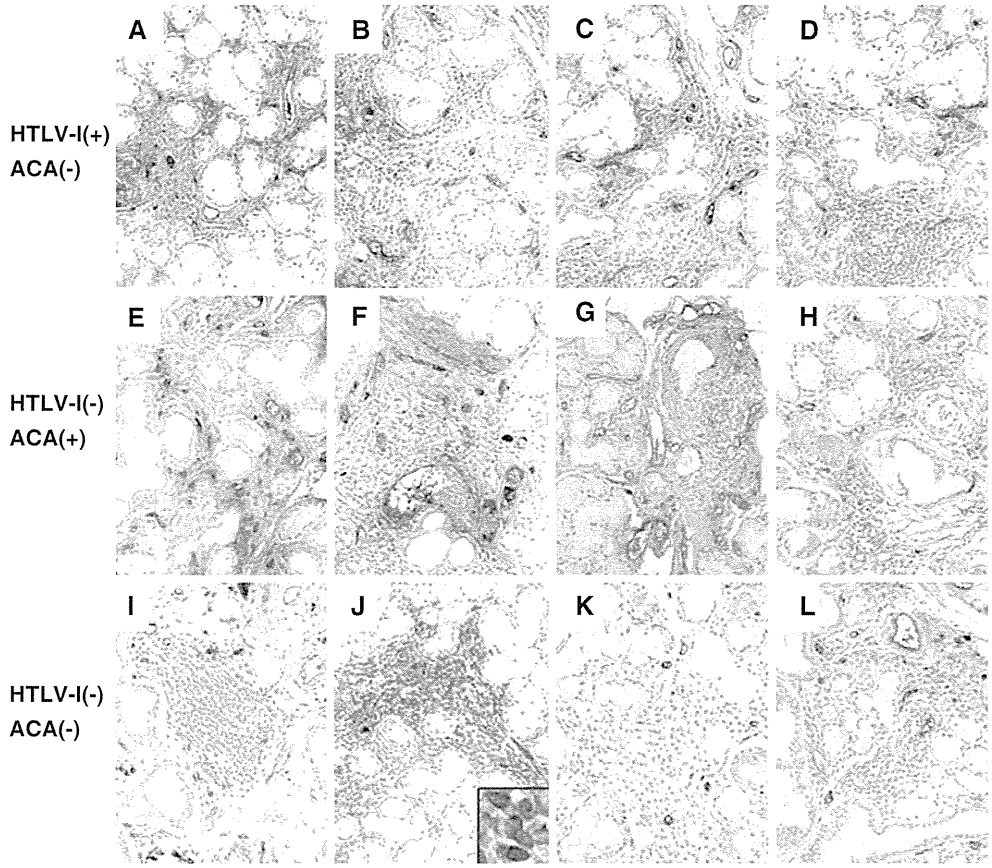

Fig. 3 Expression of transforming growth factor beta (TGF-β) in human T-cell leukemia virus type I (HTLV-I)-seropositive Sjögren's syndrome (SS) patients without anti-centromere-antibody (ACA), HTLV-I-seronegative SS patients with ACA, and HTLV-I-seronegative SS patients without ACA. Immunohistochemistry for TGF-β after epitope retrieval was performed for formalin-fixed, paraffin-embedded sections (3-μm thick) from the labial salivary gland (LSGs) using the Histofine Simple Stain Kit (Nichirei Co., Tokyo, Japan). Staining was performed for four HTLV-I-seropositive SS patients without ACA (patients A–D), four HTLV-I-seronegative SS patients with ACA (patients E–H), and four HTLV-I-seronegative SS patients without ACA (patients I–J). For patient J, TGF-β-positive MNCs are shown in the *inset* (×200). Hematoxylin was used as a counterstain

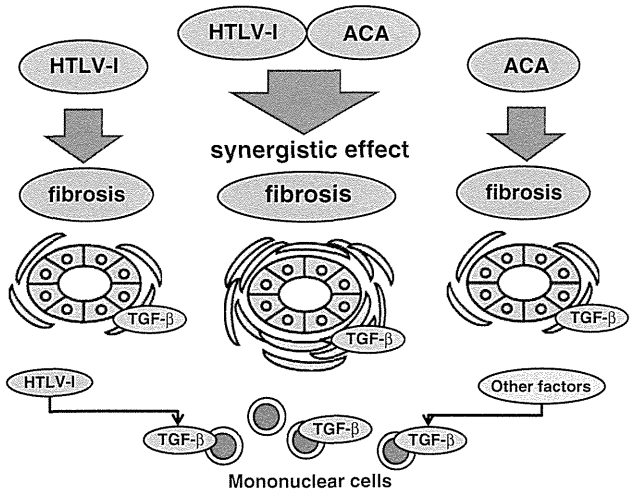

Fig. 4 Hypothesis for fibrotic alternation of salivary glands in Sjögren's syndrome (SS) patients through human T-cell leukemia virus type I (HTLV-I) infection and anti-centromere-antibody (ACA)-carrying status. From the results of the this study, HTLV-I- and ACA-carrying status induce fibrosis in labial salivary glands (LSGs). Furthermore, synergistic effects of HTLV-I infection with ACA-carrying status are assumed from the results of azocarmine with aniline blue (Azan)–Mallory staining. However, transforming growth factor beta (TGF-β), especially in mononuclear cells (MNCs), is also induced in HTLV-I infection and ACA-carrying status

In summary, we report two cases of ACA-seropositive SS found in HTLV-I-seropositive individuals and compared these patients with HTLV-I-seropositive SS patients without ACA, HTLV-I-seronegative SS patients with ACA, and HTLV-I-seronegative SS patients without ACA. The predominant characteristics were found in a patient with HAM, which was believed to have been caused by elevated HTLV-I viral load and subsequent cytokine production. Elements other than TGF-β are also suggestive of influencing fibrotic alternation of LSGs in patients with SS.

Conflict of interest None.

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国際 HIV 認知症スケールが提案されており，また，複数の検査を組み合わせた「HIV 感染者高次機能検査バッテリー」が厚労省エイズ対策研究事業 NeuroAIDS 研究班で開発され，その有用性が検証されている．

治療方針

A HIV 感染者の抗レトロウイルス療法

HIV 感染症の治療の原則は抗レトロウイルス療法で，1990 年代に逆転写酵素阻害剤 2 剤とプロテアーゼ阻害剤 1 剤の併用，いわゆる HAART が導入され，その生命予後は劇的に改善し，エイズは死に至る不治の病から長期コントロール可能な慢性疾患へと変貌した．その後も新たな作用機序をもつ薬剤の開発が進み，さまざまな組み合わせの抗レトロウイルス剤による薬物療法(combined antiretroviral therapy)が提案されている．また，その開始時期についても，副作用の低減や感染拡大を防ぐ効果を踏まえて，エイズ発症前の無症候性感染性患者においても CD4＋T 細胞数 350-500/μL を目安に早期に開始することが推奨されている．効果の判定は血中 HIV RNA 量，免疫能の回復は CD4＋T 細胞数を指標としている．しかし，現在の抗レトロウイルス療法はウイルスの増殖サイクルを阻害する薬剤であり，寿命の長いメモリー T 細胞に潜伏感染しているウイルスを駆逐することはできず，一生涯服用を続けなければならない．わが国では厚労省エイズ対策研究事業研究班の 2012 年「抗 HIV 治療ガイドライン」でエビデンスに基づいて詳しく解説している．ホームページからダウンロードできる(http://www.haart-support.jp/)．

℞ 処方例　1-3)の組み合わせのうち，いずれかを用いる．

1) ストックリン錠(600 mg)　600 mg
　ツルバダ配合錠　1 錠
　(分 1)
2) ストックリン錠(600 mg)　600 mg
　エプジコム配合錠　1 錠
　(分 1)
3) レイアタッツカプセル(150 mg)　300 mg
　ノービア錠(100 mg)　100 mg
　ツルバダ配合錠　1 錠
　(分 1　食直後)

B HIV 脳症の治療

HIV 脳症が HIV-1 の脳への感染が引き起こしている炎症であることを踏まえると抗レトロウイルス療法が原則である．HIV RNA 量の低下と CD4＋T 細胞数の回復に伴い症状や画像所見の改善を得ることができる．しかし，効果が不十分で障害を残して社会復帰できないまま長期生存する傾向にあり，今後，医療体制の整備など社会的対応が必要である．そのためにも脳症の早期発見と効果的な薬剤の選択が重要であるが，十分な効果を得るためには薬剤の中枢神経への移行が重要である．近年，化学構造，薬剤の髄液移行度，臨床的効果を加味した CPE ランク(CNS penetration-effectiveness rank)の概念が提唱され，HIV 脳症の治療薬選択の指標を提供すべく臨床研究が行われている．髄液中 HIV RNA 量の低値との相関が報告されているが，まだ十分なエビデンスは得られておらず，前述のガイドラインにも特に記述はない．**表 1** にわが国で承認されている抗レトロウイルス薬の CPE ランクを示す．

C 免疫再構築症候群への対応

HIV 感染者にみられる日和見感染症については各疾患に対する十分な化学療法が基本であるが，抗レトロウイルス療法による免疫能の回復もその治療に不可欠である．一方で，抗レトロウイルス療法の効果として，免疫能の急激な回復に伴って免疫再構築症候群が生じる可能性があることを念頭に置く必要がある．特に脳病変は致死的となる場合もあり，中枢神経系の日和見疾患の合併や既往がある患者では，日和見疾患の治療を優先し，抗レトロウイルス療法の待機や中断，あるいはプレドニゾロン 1 mg/kg/日程度の併用による炎症反応抑制が必要となる場合がある．

表1 わが国で承認されている抗HIV薬の中枢神経移行(CPEランキング)

薬剤	きわめて良好	良好	やや良好	不良
ヌクレオシド/ヌクレオチド系逆転写酵素阻害剤(NRTI)	ジドブジン(AZT)	アバカビル(ABC) エムトリシタビン(FTC)	ラミブジン(3TC)	ジダノシン(ddI) テノホビル(TDF)
非ヌクレオシド/ヌクレオチド系逆転写酵素阻害剤(NNRTI)	ネビラピン(NVP)	デラビルジン(DLV) エファビレンツ(EFV)	エトラビリン(ETR)	
プロテアーゼ阻害剤(PI)		インジナビル硫酸塩(IDV) 合剤(ロピナビル・リトナビル)(LPV/rtv)	アタザナビル(ATV) ホスアンプレナビル(FPV)	ネルフィナビル(NFV) リトナビル(rtv) サキナビル(SQV)
侵入阻止剤		マラビロク(MVC)		
インテグラーゼ阻害剤(INSTI)		ラルテグラビル(RAL)		

(McArthur JC, Steiner J, Sacktor N, et al: Human immunodeficiency virus-associated neurocognitive disorders: Mind the gap. Ann Neurol. 2010; 67: 699-714. より抜粋改変)

患者・家族への説明

抗レトロウイルス薬物療法の進歩・普及により HIV 感染症は死に至る不治の病エイズから長期コントロール可能な慢性疾患へと変貌しているが，わが国では日和見感染症で初診という，いわゆる「いきなりエイズ」の症例がしばしば経験されている．診断の遅れは抗レトロウイルス療法の開始の遅れ，ひいては HIV 脳症のリスクの上昇につながっており，HIV 感染の疑いが生じた場合は早期に抗体検査を受ける必要がある．近年は抗レトロウイルス療法により十分にコントロールされている感染者からの性行為による感染リスクは十分に低いことが示され，感染拡大防止の観点からも，無症候感染者への早期の抗レトロウイルス療法開始が勧められている．一方で，よくコントロールされている感染者においても軽微な精神神経障害の頻度は高く，きめ細かい日常行動の観察による神経障害の早期の発見と，きめ細かな薬剤の選択により重症化を防ぎ，社会生活，日常活動を維持していく必要がある．抗レトロウイルス療法の進歩は早く，治療ガイドラインもあわせて改訂されており，常に新しい治療法が受けられる体制を維持していることも大切である．HIV 脳症の進行により，問題行動や精神認知障害のために服薬の継続が困難となり，予後不良の経過をとることを理解しておかなければならない．

HTLV-Ⅰ関連脊髄症

HTLV-I-associated myelopathy (HAM)

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疾患概念

A 病態

HTLV-Ⅰ関連脊髄症(HAM)は HTLV-Ⅰ感染によって惹起される脊髄の慢性炎症性疾患である．病変の主座は下部胸髄の両側側索にある．発症機序としては，脊髄に浸潤してくる HTLV-Ⅰ感染 CD4 陽性 T 細胞と，それに対する HTLV-Ⅰ特異的 CD8 陽性細胞傷害性 T 細胞との相互作用の結果生じる周囲脊髄組織の破壊，いわゆるバイスタンダーメカニズムが想定されている．発症年齢のピークは 40-50 歳くらいであるが，若年・高齢発症もある．孤発例が多いが，家族内発症も時にみられる．男女比は約 1：2 と女性に多い．HTLV-Ⅰの感染経路としては母乳を通しての母子垂直感染が多いが，輸血(1986

年以降の新たな輸血による発症はなくなっている)や夫婦間感染もある.

B 経過・予後

基本型は緩徐進行性である.再発・寛解は呈さない.ただ,時に亜急性に進行する例や進行が停止する例がある.

症候

神経因性膀胱による排尿障害を伴った痙性対麻痺を呈する.両下肢のつっぱり感などで発症することが多いが,時に排尿障害が先行することもある.両下肢の錐体路徴候としての痙縮,病的反射,クローヌス,痙性歩行を認める.ただし,痙縮の程度にはかなり個人差がみられる.感覚障害は程度は強くはないが,下肢のしびれ感,じんじん感,あるいは痛みなどの感覚異常としての訴えがしばしば認められる.他覚的所見として捉えられないことも少なくなく,また脊髄レベルを伴わないことが多い.自律神経障害として上記排尿障害以外に,頑固な便秘,脊髄レベル以下の発汗低下,勃起障害などがしばしば認められる.時に末梢神経障害を伴うことがある.かなり罹病期間が長い症例でも,上肢については病的反射はみられても機能障害はきたさないことが多い.ぶどう膜炎やシェーグレン症候群 Sjögren syndrome などのほかの炎症性疾患の合併にも留意する必要がある.

検査

血清・髄液で抗 HTLV-Ⅰ抗体陽性を認める.一般的に血清中での本抗体価は高値を示す.陽性の有無は,特に抗体価が低い場合には,ウエスタンブロット法で確認することが望ましい.末梢血では HTLV-Ⅰプロウイルス量が多く(HAM 発症の最大危険因子),血清可溶性 IL-2 受容体値や髄液ネオプテリン値がしばしば高値を示す.また,末梢血単核球の PHA などのレクチンに対する幼若化試験で刺激指数(stimulation index ; SI)がしばしば低値を示す.画像検査では,特異的な所見は認められないが,罹病期間の長い症例では胸髄萎縮を認め,また進行の早い例では時に脊髄腫脹を認めることがある.

診断

緩徐進行性の経過で排尿障害を伴った痙性対麻痺を示し,血清・髄液中抗 HTLV-Ⅰ抗体陽性で,脊髄圧迫性病変あるいは多発性硬化症などのほかの疾患が除外されるときに確定診断される.比較的急速に進行する例では,抗アクアポリン(AQP)4 抗体を測定し視神経脊髄炎を除外する必要がある.

治療方針

HAM の理想的な治療は,末梢血からの HTLV-Ⅰの排除であるが,現時点でそのような治療法はない.治療法は確立していないが,治療方針としては「炎症を抑制することによって,その後の進行を抑えること」を目的とする免疫修飾療法が主体となる.加えて,抗痙縮薬や排尿改善薬の投与,さらには筋力低下の予防,筋力維持,そして筋拘縮予防としてのリハビリテーションを対症療法として行う.現在,HAM の活動性の指標となる確固たるバイオマーカーはないが,末梢血 HTLV-Ⅰプロウイルス量・可溶性 IL-2 受容体値や髄液抗 HTLV-Ⅰ抗体価・ネオプテリン値が高値を示すほど,炎症の活動性が高く,運動機能障害の進行が早いとされ,このような症例に対しては積極的な免疫修飾療法が推奨される.

A 免疫修飾療法

1. 副腎皮質ステロイド療法

亜急性に経過する例ではステロイドパルス療法が有効な場合がある.

℞ 処方例

(内服薬)

プレドニン錠(5 mg)　30-80 mg(目安として 1-2 mg/kg)　分 2　朝・昼食後　1-2 か月連日または隔日投与 保外 1-2 か月後より 5-10 mg の隔日投与にまで徐々に減量し継続していくか,または 6-12 か月後には中止

(注射薬)

ソル・メドロール注(500 mg)　1 回 500-1,000 mg　ソリタ-T3 号または 5% ブドウ糖 500

mL に混和し，1日1回　点滴静注　3日間連日を1クールとして，必要に応じて数クール施行 保・外
ステロイド療法として，経口プレドニン療法を適宜追加

薬剤の漸減によって，一般的に症状が再度悪化することが多く，長期にわたる治療を必要とする場合が多い．したがって，消化性潰瘍，耐糖能異常，高血圧，骨粗鬆症，精神症状などの重篤な副作用の出現に注意を要する．副作用対策として，消化性潰瘍に対してはH2受容体拮抗薬，プロトンポンプ阻害薬などを，骨粗鬆症に対してはビスホスホネート製剤やビタミンD製剤などを投与する．また，日和見感染にも注意を要する．

2. インターフェロンα療法

HAMに対する治療薬として唯一，厚生労働省によって認可されている薬剤である．ただし，保険適用がとれているのはスミフェロン®のみである．本薬剤は免疫修飾作用に加えて抗ウイルス作用をもっている可能性がある．

Px 処方例
スミフェロン注バイアルまたはスミフェロン注DS　1回300万IU　1日1回　筋注または皮下注　連日

まずは上記の4週間投与が標準的な治療法である．ただし，症例に応じて投与期間・投与間隔は適宜調整する．投与中止で再度症状が悪化する例も多く，長期に投与(例えば1-2回/週)されている症例も少なくない．副作用については，頻度の多いものとしては発熱，全身倦怠感などの感冒様症状である．これらは一般的に，連日投与の場合1-2週間で消失していくが非ステロイド系消炎鎮痛薬を併用する．骨髄抑制や肝機能障害が起こることがあるので，定期的な血液検査が必要である．自己免疫性肝炎や小柴胡湯投与中の患者には禁忌である．間質性肺炎(特に小柴胡湯併用時)，抑うつ状態といった精神症状，糖尿病，自己免疫疾患などの重篤な副作用の出現には注意を要する．

3. 間欠的ビタミンC大量療法

Px 処方例
ハイシー顆粒(25%)　140-160 mg/kg　分1-2　食後　3-5日経口投与，2-3日休薬の間欠投与を繰り返す 保・外

休薬期間を設定する理由は，好中球減少症の出現防止のためである．

B 対症療法

1. 痙縮に対して

Px 処方例　下記のいずれかを用いる．
1) ミオナール錠(50 mg)　150-300 mg　分3　毎食後
2) テルネリン錠(1 mg)　3-6 mg　分3　毎食後
3) リオレサール錠(5 mg)　15-30 mg　分3　毎食後
4) ダントリウムカプセル(25 mg)　25-75 mg　分2-3　食後

痙縮が強い場合に使用するが，脱力の増悪に注意する．薬物治療抵抗性の場合，リオレサールの体内留置ポンプによる髄腔内持続投与が有効な場合がある．

2. 神経因性膀胱に対して

症例ごとに低活動型膀胱，過活動型膀胱，あるいは膀胱排尿筋-尿道括約筋協調不全など，多彩な病型を呈しかつ経過とともに病型が変化しうるので，治療にあたっては専門の泌尿器科主治医と連携することが望ましい．薬剤によるコントロール困難な症例も多く，その場合は自己導尿の導入となる．

a. 蓄尿障害

頻尿・尿失禁を呈する過活動膀胱には抗コリン薬を使用する．

Px 処方例　下記のいずれかを用いる．
1) バップフォー錠(10 mg)　10-20 mg　分1　食後
2) ステーブラ錠(0.1 mg)またはウリトス錠(0.1 mg)　0.2 mg　分2　食後
3) ベシケア錠(5 mg)　5 mg　分1　食後
4) デトルシトールカプセル(4 mg)　4 mg

分1　食後
5) プラダロン錠(200 mg)　600 mg　分3　毎食後
6) ボラキス錠(1 mg)　6-9 mg　分3　毎食後
7) ベタニス錠(25・50 mg)　50 mg　分1　食後

HAMでしばしばみられる膀胱排尿筋-尿道括約筋協調不全への単独使用は注意を要する．副作用として口渇，便秘などがある．最近，より副作用が少ないとされるβ_3作動薬ベタニスが承認を取得している．

b. 排出障害

尿道括約筋の過緊張の抑制にα_1遮断薬を，低活動型の膀胱排尿筋に対してコリン作動薬を使用する．

① α_1遮断薬

Rx 処方例　下記のいずれかを用いる．

1) ハルナールD錠(0.2 mg)　0.2 mg　分1　食後 保・外
2) エブランチルカプセル(15 mg)　30-60 mg　分2　食後 保・外
3) フリバス錠(25 mg)　25 mg　分1　食後 保・外
4) ミニプレス錠(0.5 mg)　1.5 mg　分3　食後 保・外

血圧低下，起立性低血圧，立ちくらみなどに注意する．

② コリン作動薬

Rx 処方例

ウブレチド錠(5 mg)　5 mg　分1　食後 保・外

下痢，発汗などに注意する．

患者・家族への説明

・絨毯などのちょっとした段差や下り坂でのつまずきに注意することを説明する．
・筋力低下の予防，筋力維持，そして筋拘縮予防のためのリハビリテーションの重要性を説明する．
・HAMは感染性疾患ではあるが，HTLV-Ⅰは空気感染はしないので，通常の社会生活では感染はしないこと，また遺伝性疾患でもないことを説明する．
・HAMは2009年4月から厚生労働省により難病として認定を受けている．難病情報センター(http://www.nanbyou.or.jp/sikkan/128.htm)や神経難病ネットワークから情報を得ることができることを説明する．
・HTLV-1研究班合同委員会が運営者となり，HTLV-Ⅰ情報サービスのサイト(http://www.htlv1joho.org/)が開設されていて，そのサイトにHAMに関する冊子「HAMと診断された患者さまへ」が掲載されていることを説明する．
・HAM患者登録システムとして「HAMねっと」(http://www.hamtsp-net.com)が開設されていることを説明する．

化膿性髄膜炎

purulent meningitis

亀井　聡　日本大学医学部主任教授・内科学系神経内科学分野

疾患概念

A 定義

髄膜炎とは，くも膜・軟膜およびその両者に囲まれたくも膜下腔の炎症を示す．髄膜炎は持続する頭痛と発熱を主徴とし，髄膜刺激症候を認め，髄液細胞数の増加を示す．主な病因として，細菌，結核菌，真菌，ウイルスなどがあるが，一般に，化膿性髄膜炎は細菌性髄膜炎のことを意味し，結核性や真菌性は含まない．

B 頻度・病態

本邦における年間の発症頻度は約1,500人(小児が3/4で，成人が1/4)と推定されている．本症の病態は，細菌の直接的侵襲だけでなく，細菌の微小構造物(例えば，細胞壁など)や，産生産物(例えば，エンドトキシン)による宿主の免疫応答を介したサイトカイン・ケモカイン・酸化窒素などのカスケードによる炎症過程の亢進が大きく関与する(図1)．これら免疫応答の制御も治療上重要である．本症の感染経路は，①菌血症からの血

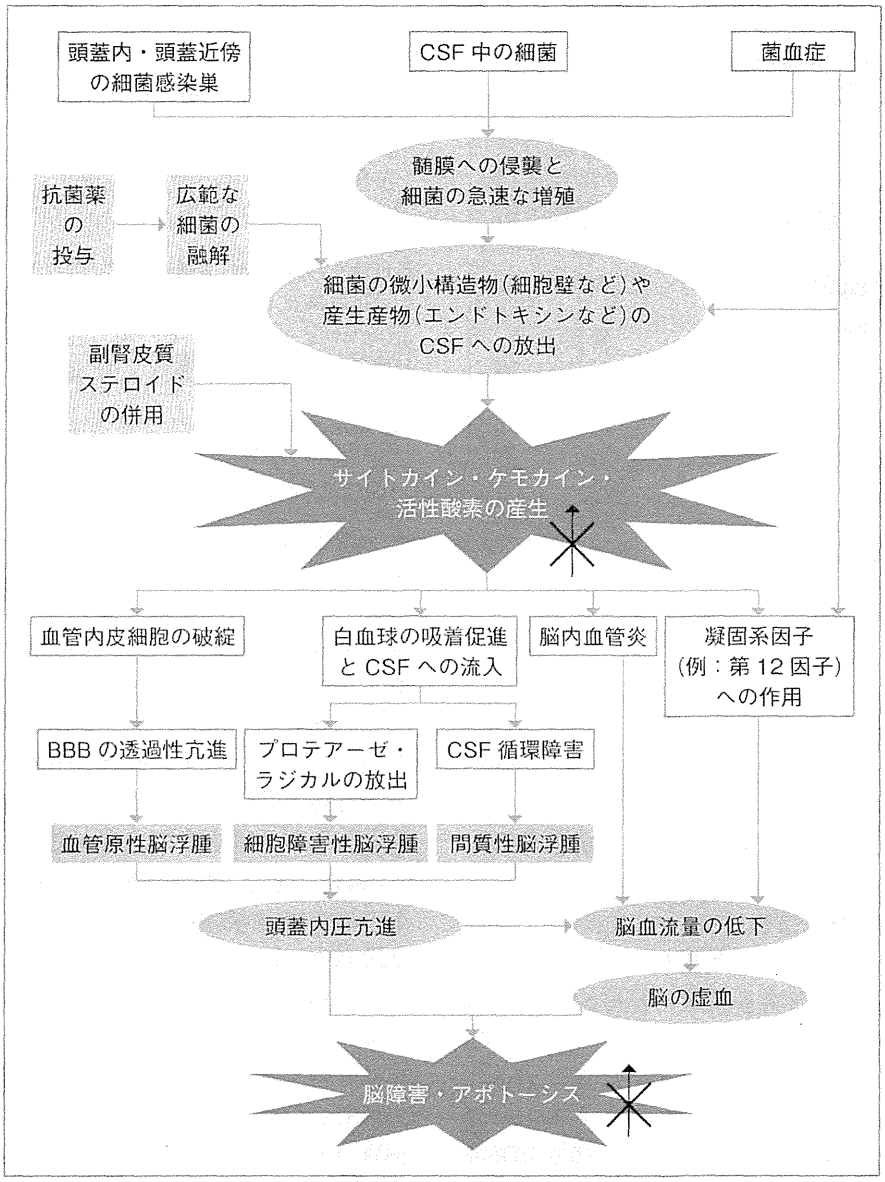

図1 細菌性髄膜炎の病態

CSF：髄液，BBB：血液脳関門．

病原菌が髄膜へ播種し急速な増殖をすると，細菌の細胞壁や膜関連産物(タイコ酸，ペプチドグリカン，エンドトキシンなど)が髄液内へ遊離する．抗菌薬の投与は，細菌壁に作用し急速な菌融解を呈するが，その際に壁産物の放出が増強される．これらの産物は，腫瘍壊死因子(TNF)，インターロイキン(IL)-1β，IL-6，血小板活性化因子(PAF)，酸化窒素，プロスタグランディンなど炎症性サイトカイン・ケモカイン・活性酸素の産生を惹起する．これらの放出は，脳血管内皮細胞の破綻や白血球の吸着促進受容体を活性化させ，血液脳関門の透過性亢進による血管原性脳浮腫やプロテアーゼやラジカルの放出による細胞障害性脳浮腫を惹起する．さらに，蛋白濃度や細胞数の増加により，粘稠度は上昇し，髄液循環障害を起こし間質性脳浮腫が出現する．以上より脳浮腫は増強し，頭蓋内圧亢進を呈する．頭蓋内圧亢進は，髄液循環障害，脳内の虚血，脳の代謝および脳血流の変化をきたし，脳障害やアポトーシスが進行する．一方，末梢血管拡張作用のあるメディエーターを介し血管炎の併発からも脳内の虚血をもたらす．抗菌薬と副腎皮質ステロイドを併用すると，TNF-αやIL-1βのmRNA転写およびプロスタグランディンやPAFの産生を抑制し，脳浮腫を軽減し酸化窒素の産生が抑えられ，結果として脳障害が軽減される．

PLOS ONE

Familial Clusters of HTLV-1-Associated Myelopathy/Tropical Spastic Paraparesis

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Abstract

Objective: HTLV-1 proviral loads (PVLs) and some genetic factors are reported to be associated with the development of HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). However, there are very few reports on HAM/TSP having family history. We aimed to define the clinical features and laboratory indications associated with HAM/TSP having family history.

Methods: Records of 784 HAM/TSP patients who were hospitalized in Kagoshima University Hospital and related hospitals from 1987 to 2012 were reviewed. Using an unmatched case-control design, 40 patients of HAM/TSP having family history (f-HAM/TSP) were compared with 124 patients suffering from sporadic HAM/TSP, who were admitted in series over the last 10 years for associated clinical features.

Results: Of the 784 patients, 40 (5.1%) were f-HAM/TSP cases. Compared with sporadic cases, the age of onset was earlier (41.3 vs. 51.6 years, $p<0.001$), motor disability grades were lower (4.0 vs. 4.9, $p=0.043$) despite longer duration of illness (14.3 vs. 10.2 years, $p=0.026$), time elapsed between onset and wheelchair use in daily life was longer (18.3 vs. 10.0 years, $p=0.025$), cases with rapid disease progression were fewer (10.0% vs. 28.2%, $p=0.019$), and protein levels in cerebrospinal fluid (CSF) were significantly lower in f-HAM/TSP cases (29.9 vs. 42.5 mg, $p<0.001$). There was no difference in HTLV-1 PVLs, anti-HTLV-1 antibody titers in serum and CSF, or cell number and neopterin levels in CSF. Furthermore, HTLV-1 PVLs were lower in cases with rapid disease progression than in those with slow progression in both f-HAM/TSP and sporadic cases.

Conclusions: We demonstrated that HAM/TSP aggregates in the family, with a younger age of onset and a slow rate of progression in f-HAM/TSP cases compared with sporadic cases. These data also suggested that factors other than HTLV-1 PVLs contribute to the disease course of HAM/TSP.

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Introduction

HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) is characterized by slow progressive spastic paraparesis and positivity for anti-HTLV-1 antibodies in both serum and cerebrospinal fluid (CSF) [1,2]. Worldwide, at least 10–20 million people are infected with HTLV-1 [3]. However, although the majority of infected individuals remain lifelong asymptomatic carriers, approximately 2%–5% develop adult T-cell lymphomas [4,5] and another 0.25%–3.8% develop HAM/TSP [1,2]. Although the mechanisms underlying the development of HAM/TSP are not fully understood, several risk factors are closely associated with HAM/TSP. In particular, HTLV-1 proviral loads (PVLs) are significantly higher in HAM/TSP patients than in asymptomatic carriers and are also higher in genetic relatives of HAM/TSP patients than in non-HAM-related asymptomatic carriers [6]. Host genetic factors, including human leukocyte antigen (HLA) and non-HLA gene polymorphisms affect the occurrence of HAM/TSP [7], indicating that HTLV-1 PVLs and genetic backgrounds may influence individual susceptibility to HAM/TSP. Although several reports of familial adult T-cell lymphoma have been published [8,9], to our knowledge, there is only one case report of patient with HAM/TSP having family history (f-HAM/TSP) [10]. Hence, little is known about the prevalence and character of f-HAM/TSP cases. In this study, the characteristic clinical and laboratory features of f-HAM/TSP cases are defined and compared with those of sporadic cases.

Methods

Ethics Statement

This study was approved by the Institutional Review Boards of Kagoshima University. All participants provided written informed consent.

Design

We used an unmatched case-control design to identify the phenotypic features of f-HAM/TSP. f-HAM/TSP cases were identified as patients with multiple family members suffering from HAM/TSP. Controls were defined as HAM/TSP patients who were not genetically related to other HAM/TSP patients.

Subjects

f-HAM/TSP cases were extracted from our database of individuals diagnosed with HAM/TSP in Kagoshima University Hospital and related hospitals from 1987 to 2012. Controls included consecutive patients with sporadic HAM/TSP who were evaluated in our department between January 2002 and June 2012. HAM/TSP was diagnosed according to the World Health Organization diagnostic criteria, and the updated criteria of Castro-costa Belem [11]. Clinical information was obtained from the medical records of patient attendance at our hospital. In other cases, clinical data were obtained from the clinical records of patients or directly from the referring clinicians. Clinical variables included sex, age, age of onset, and initial symptoms. Neurological disabilities were assessed using Motor Disability Grading (MDG), modified from the Osame Motor Disability Scale of 0 to 10, as reported previously [12]. Motor disability grades were defined as follows: 5, needs one-hand support while walking; 6, needs two-hand support while walking; and 7, unable to walk but can crawl. We used a different assessment for the subgroup of more than grade 6 because their disease state significantly interfered with their lifestyle and necessitated the use of wheelchairs in daily life. The subgroup of patients with rapid progression was defined by deterioration of motor disability by more than three grades within two years. Anti-HTLV-1 antibody titers in serum and CSF were detected using enzyme-linked immunosorbent assays and particle agglutination methods (Fijirebio Inc, Tokyo, Japan). HTLV-1 PVLs in peripheral blood mononuclear cells (PBMCs) were assayed using quantitative PCR with the ABI PRISM 7700TM sequence detection system as reported previously [6].

Statistical Analysis

Data were analyzed using SPSS-20 (SPSS, Chicago, Illinois). Statistical analyses were performed using parametric (t-test) and non-parametric tests (Mann–Whitney test) for continuous variables and χ^2 (Pearsonχ^2 test/Fisher exact test) for categorical variables. Significant differences were then adjusted for potential confounders (age and sex) using multiple linear regression analysis. Survival was estimated according to the Kaplan–Meier method. The final endpoint was defined by a MDG score of 6. Patients with MDG scores of 6 almost wheelchair bound in daily life. The log rank test was used in Kaplan–Meier analyses. Differences were considered significant when $p<0.05$.

Results

Clinical characteristics of f-HAM/TSP

Of the 784 patients diagnosed with HAM/TSP between January 1987 and June 2012, 40 (5.1%) were f-HAM/TSP. The sex ratio was 33 males : 7 females. Of these 40 cases, 10 had parents or children (25.0%), 27 had siblings (67.5%), and three had other relatives (7.5%) diagnosed with HAM/TSP. Three individuals from one family were diagnosed with HAM/TSP, whereas only two individuals were diagnosed with HAM/TSP in all other families. In f-HAM/TSP cases, the age of onset was earlier (41.3 vs. 51.6 years, $p<0.001$), cases with rapid progression were fewer (10.0% vs. 28.2%, $p = 0.019$), motor disability grades were lower (4.0 vs. 4.9, $p = 0.043$) despite longer duration of illness (14.3 vs. 10.2 years, $p = 0.026$), and time elapsed between onset and wheelchair use in daily life was longer (18.3 vs. 10.0 years, $p = 0.025$) compared with sporadic cases. Sex and initial symptoms did not differ significantly between f-HAM/TSP and sporadic cases (Table 1). Twelve patients of f-HAM/TSP, and 38 of the 128 sporadic cases reached endpoint MDG scores of 6. Significant differences were then adjusted for potential confounders (age and sex) using multivariate analysis. Age of onset, duration of illness, MDG scores, and time elapsed between onset and wheelchair use in daily life remained significantly different after multivariate analysis (Table 1). The proportion of patients with rapid progression did not differ significantly between the groups, although there was a trend toward a higher proportion in sporadic cases. Kaplan–Meier analyses revealed that approximately 30% of both f-HAM/TSP and sporadic cases needed a wheelchair in daily life in 15 years after onset, and approximately 50% of patients from both groups needed it in 20 years after onset (Figure 1). Although sporadic patients needed wheelchairs earlier in most cases, the difference in the ratio of the patients with MDG score above six was not statistically significant between the groups. Finally, we compared differences in the age of onset between parent–child and sibling cases in f-HAM/TSP cases. Age of onset in parent–child f-HAM/TSP cases was significantly younger than that in sibling f-HAM/TSP cases (29.9 ± 10.0 vs. 45.1 ± 13.0 years, $p = 0.002$).

Laboratory parameters and PVLs in f-HAM/TSP cases

Protein levels in CSF were significantly lower in f-HAM/TSP cases than in sporadic cases (29.9 vs. 42.5 mg/dl, $p<0.001$). This difference in CSF protein level remained significant after multivariate analysis. Anti-HTLV-1 antibody titers in serum and CSF, and cell numbers and neopterin levels in CSF were not significantly different between two groups. Moreover, HTLV-1 PVLs did not differ significantly. (Table 2).

Clinical and laboratory findings in patients with rapid disease progression

Previous studies suggest that an older age of onset is associated with rapid disease progression. Similar findings are found in the present study. The percentage of rapid progression tended to increase with older age of onset in both f-HAM/TSP and sporadic groups (Figure 2). We compared the characteristics of 124 sporadic HAM/TSP patients with rapid and slow progression who were admitted to Kagoshima University Hospital in series during the last 10 years (Table 3). Patients with rapid progression were significantly older at onset than those with slow progression (62.3 vs. 47.4 years, $p<0.001$), although sex and initial symptoms did not differ significantly between rapid and slow progression groups. However, the time elapsed between onset and wheelchair use in daily life was markedly shorter among patients with rapid progression (1.5 vs. 14.4 years, $p<0.001$). Cell numbers, protein levels, and anti-HTLV-1 antibody titers in CSF were significantly higher in patients with rapid progression than in those with slow progression (11.6 vs. 3.2, $p<0.001$; 55.3 vs. 36.7 mg/dl, $p<0.001$; 1,251 vs. 416, $p<0.014$, respectively). Interestingly, HTLV-1 PVLs were significantly lower in patients with rapid progression than in those with slow progression (370 vs. 1,245 copies, $p<0.001$). Furthermore, we compared the differences between women and men in patients with rapid progression because the reason remains unknown why HAM/TSP is common in female