Intermittent high-dose vitamin C therapy in HAM

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Abstract
The efficacy of intermittent high-dose vitamin C therapy was evaluated in seven patients with HTLV-I-associated myelopathy (HAM). All HAM patients responded well to this therapy without serious side effects. Grade of disability score improved at 9-7 (SD 5-8) months after the therapy from 7-1 (3-3) to 3-6 (2-0) (p < 0.01). Serum immunosuppressive acidic protein was elevated before and decreased after the therapy from 747 (316) to 398 (86) μg/ml (p < 0.05), suggesting favourable immunomodulatory action of vitamin C therapy in HAM patients.

Progressive spastic paraparesis of unknown cause was, for a long time, a common neurological problem in both temperate and tropical regions. A major advance in the understanding of this condition occurred when Gessain et al demonstrated that the human T cell lymphotropic type 1 retrovirus (HTLV-I) was associated with tropical spastic paraparesis. A similar neurological condition has been described in Japan, where it is called HTLV-I-associated myelopathy (HAM). Although some previous studies have suggested that an immunological mechanism is responsible for the pathogenesis of HAM, it is still not known how HTLV-I infections influence the immune system in HAM patients, and how they are linked to myelopathy. Furthermore, the medical management of HAM remains to be determined. In this study, we evaluated for the first time the efficacy of intermittent high-dose vitamin C therapy in patients with HAM.

Patients and methods
Between November 1990 and May 1992, seven patients with HAM (four men and three women, aged 36 to 81 years), who were given a daily oral dose of 35-40 mg/kg of vitamin C for three to five successive days followed by a two-day withdrawal period, were followed for a mean period of 9-7 (SD 5-8) months after the therapy. The diagnostic criteria of HAM proposed by Osame et al were adopted. These criteria are: (1) chronic progressive myelopathy of adult onset, (2) high titres of antibody against HTLV-I in serum and CSF, (3) predominantly symmetrical upper motor neuron disorder, with mild sensory and bladder dysfunctions, and (4) presence of adult T cell leukemia-like cells in the peripheral blood. The neurological condition was steady in three patients and had worsened in four for at least two to three months before entry to this study. During the study period (beginning one month before vitamin C therapy), no attempt was made to modify other treatment regimens. Each patient visited our outpatient clinic at two week intervals, and general clinical and neurological conditions were checked by a specially trained neurologist (AK), who had no knowledge of the specific therapeutic regimens used. At each visit, muscle strength in both the lower limbs was evaluated by muscle manual testing (MMT). For this, muscle strength was graded on a 5-point scale as follows: 0 = normal, 1 = good, 2 = fair, 3 = poor, 4 = zero. Muscle strength was graded in seven muscles in each lower limb: iliopsoas, quadriceps femoris, hamstrings, tibiais anterior, gastrocnemius, toe extensor, and toe flexor. Scores for each muscle in both lower limbs were summed. The therapeutic efficacy was also evaluated using the 13-grade disability scoring (DS) system proposed by Osame et al, short somatosensory evoked potentials (SSEP) elicited by tibial nerve stimulation, and immunological parameters before and during the follow up visit (2-0 to 18 months after the therapy). Examined immunological parameters (normal range) included IgA (82-363 mg/dl), IgG (890-1744 mg/dl), and IgM (52-298 mg/dl) in the serum, HTLV-I antibody titre in the CSF (negative) and serum (negative), OKT4/OKT8 ratio in the peripheral blood (0.6-2.9), CSF-IgG index (0.3-0.75), and immunosuppressive acidic protein (IAP) in the serum (<500 μg/ml). Results were expressed as the mean (SD). The data were analysed statistically using paired t test with the level of significance set at p < 0.05.

Results
All HAM patients responded well to intermittent high-dose vitamin C therapy. In each patient, MMT improved gradually at each visit (fig 1). Upon evaluation by the DS scoring system, six patients were excellent responders (DS improvement ≥ two grades) and one was a good responder (DS improvement of one grade). As a whole, the grade of DS was decreased at 9-7 (5-8) months after the therapy from 7-1 (3-3) (baseline) to 3-6 (2-0)
Duration of post-treatment (months)

Figure 1  Serial changes in MMT score during vitamin C therapy in HAM patients.

Case 1
Cz-Fz
Th12-Iliac crest
Pre-treatment
Case 2
Cz-Fz
Th12-Iliac crest
Case 3
Cz-Fz
Th12-Iliac crest
Case 4
Cz-Fz
Th12-Iliac crest
Post-treatment
12 M after
Cz-Fz
Th12-Iliac crest
N20 (21-6) P37 (41-4)
3 M after
Cz-Fz
Th12-Iliac crest
N20 (22-0) P37 (50-2)
14 M after
Cz-Fz
Th12-Iliac crest
N20 (21-6) P37 (42-6)
6 M after
Cz-Fz
Th12-Iliac crest
N20 (21-4) P37 (42-8)

Figure 2  SSEPs obtained from four patients with HAM before and during vitamin C therapy. In cases 1 and 3, peak latency of N20 was not recorded before therapy, but it appeared afterwards; the prolonged peak latency of P37 improved after the therapy. In cases 2 and 4, prolongation of peak latency of N20 and P37 did not change, but the amplitude increased after the therapy.

SSEPs were obtained before and after the therapy in four of the patients (fig 2). On SSEP before therapy, all the patients showed abnormally prolonged P37 peak latency. N20 was not recorded in two patients. After the therapy, N20 appeared and prolonged P37 peak latency improved in these two patients.

Immunological parameters before and after vitamin C therapy are shown in the table. Immunoglobulin concentrations, HTLV-I antibody titre in serum, and OKT4/OKT8 ratio in the peripheral blood did not change. There was also no alteration of the CSF-HTLV-1 antibody titre. However, CSF-IgG index and serum IAP were elevated before and decreased after therapy from 1·86 (1·18) to 0·98 (0·47) (p < 0·01) and from 747 (316) to 398 (86) µg/ml (p < 0·05), respectively.

After confirmation of the therapeutic effects, four of our patients (cases 1, 3, 4, 6) underwent a vitamin C on-off study, which demonstrated a positive dose response (p < 0·01), indicating an excellent clinical outcome.
Table

| Immunological parameters of seven HAM patients before and after vitamin C therapy |
|---|---|---|---|---|---|
| | Serum anti-HTLV titer | CSF anti-HTLV titer | CSF IgG index | Serum IAP (µg/ml) | OKT4/OKT8 in blood |
| | Before | After | Before | After | Before | After | Before | After | Before | After |
| 1 | 10 | 4096 | 4096 | 32 | 32 | 0.71 | 0.50 | 1110 | 403 | 4-99 | 5-09 |
| 2 | 4 | 20480 | 40960 | 512 | 256 | 1.29 | 0.81 | 380 | 315 | 3-00 | 2-90 |
| 3 | 2 | 10240 | 10240 | 256 | 256 | 1.20 | 0.60 | 975 | 1462 | 1-80 | 1-50 |
| 4 | 4 | 20480 | 40960 | 256 | 256 | 1.20 | 1.70 | NA | NA | NA | NA |
| 5 | 3 | 0.76 | 3 | 0.80 | 3.00 | 3-20 | 2 | 508 | 520 | 3-24 | 2-50 |
| 6 | 0.76 | 3 | 0.80 | 3.00 | 3-20 | 2 | 508 | 520 | 3-24 | 2-50 |
| 7 | 0.76 | 3 | 0.80 | 3.00 | 3-20 | 2 | 508 | 520 | 3-24 | 2-50 |
| Mean | 4-85 | 22820 | 80 | 347 | 508 | 520 | 3-24 | 2-50 |
| SD | 3-80 | 344 | 735 | 660 | 3-24 | 2-50 |

IAP = immunosuppressive acidic protein; M = male; F = female; NA = measurement not available; NS = non-significant.

Discussion

Immunological abnormalities in patients with HAM have been disclosed by several investigators. A favourable response of HAM patients to immunomodulatory therapeutics has been reported, which also suggests an important role of immune mechanisms in the disease expression. Recently, the efficacy of vitamin C therapy for AIDS patients has been suggested, but efficacy in HAM patients has not yet been studied. Because AIDS and HAM are diseases with interrelated factors, we studied the effects of intermittent high dose vitamin C therapy on HAM patients and found that it was an effective treatment. The improvement in MMT by four of the patients was remarkable; from initial scores of 56-29 to under 10 in roughly 2 months. Lower limb SSEPs, which are frequently abnormal in HAM patients, improved after vitamin C therapy in our patients as shown in figure 2.

The precise mechanism(s) by which high dose vitamin C therapy improves HAM remains unknown, but firstly, its immunomodulatory action should be kept in mind when considering the behaviour of serum IAP levels in response to the therapy. IAP is one of several immunosuppressive substances isolated from ascitic fluid and serum of cancer patients, and is reported to be produced mainly by macrophages. Thus, it could be expected that the serum IAP levels can serve as a marker of monocyte or macrophage activation. It has been described that the level of IAP increased in the serum of patients with inflammatory or immunopathological neurological diseases. In the present study, we demonstrated for the first time that high serum IAP levels were present in HAM patients before treatment. Previous study has suggested the important role of the macrophages for autologous proliferation of peripheral lymphocytes in HAM patients. Thus, it is possible that elevated serum IAP levels in HAM patients would have reflected abnormally activated macrophages and might be related to enhanced autologous proliferation of peripheral blood lymphocytes. During vitamin C therapy, serum IAP levels decreased significantly, which should have reflected subsiding activity of the macrophages. The role of vitamin C on immune defence during infectious diseases including viral infection has been widely investigated without definite conclusions.

Further studies appear to be warranted to elucidate the mechanism underlying the favourable effects of vitamin C on HAM.

Our observation seems to be important because it might be linked to pathological observations of macrophage accumulation and functional abnormality at the lesion sites in the spinal cord. Recently, a sensitive method for determining the level of intrathecal IAP has been developed. Assay of CSF-IAP using this test should provide more useful information on the immunopathological events occurring within the central nervous system in HAM patients.

We chose an intermittent vitamin C dosage regimen because we have found that continuous vitamin C administration seems to induce bacterial infections. Intermittent therapy seemed to reduce this complication. For ethical reasons, this study lacked a placebo controlled group. While this may prevent us from drawing any firm conclusions, our observations are of particular interest in the light of published reports which indicate that spontaneous improvement to the degree we have attained is unknown in HAM. In addition, the vitamin C on-off study clearly demonstrated a positive dose response relationship.
These observations further confirmed the efficacy of high dose vitamin C therapy in HAM patients.

4 Macatonia SE, Cruickshank JK, Rudge P, Knight SC. Dendritic cells from patients with tropical spastic paraparesis are infected with HTLV-I and stimulate autologous lymphocyte proliferation. AIDS Research and Human Retroviruses 1992;8:1699-706.