SHORT REPORT

Intermittent high-dose vitamin C therapy in patients with HTLV-I associated myelopathy

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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.

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Progressive spastic paraparesis of unknown cause was, for a long time, a common neurological problem in both temperate and tropical regions.[1] A major advance in the understanding of this condition occurred when Gessain *et al*[2] 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).[3] Although some previous studies have suggested that an immunological mechanism is responsible for the pathogenesis of HAM,[1 4–6] 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.

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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*[6] 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, tibialis 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*,[6] short somatosensory evoked potentials (SSEP) elicited by tibial nerve stimulation,[7] 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)[8 9] 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)

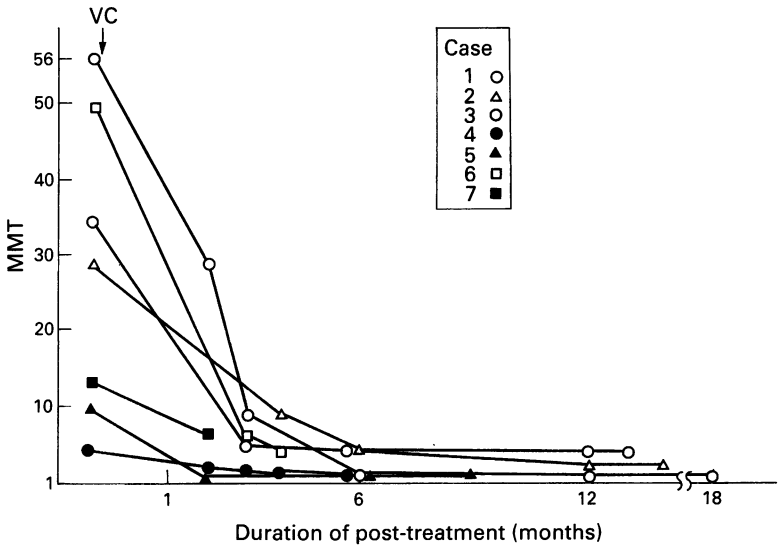

Figure 1 Serial changes in MMT score during vitamin C therapy in HAM patients.

($p < 0.01$), indicating an excellent clinical outcome.

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-I antibody titre. However, CSF-IgG index and serum IAP were elevated before and decreased after therapy from 1·86 (1·18) to 0·88 (0·47) ($p < 0.1$) 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

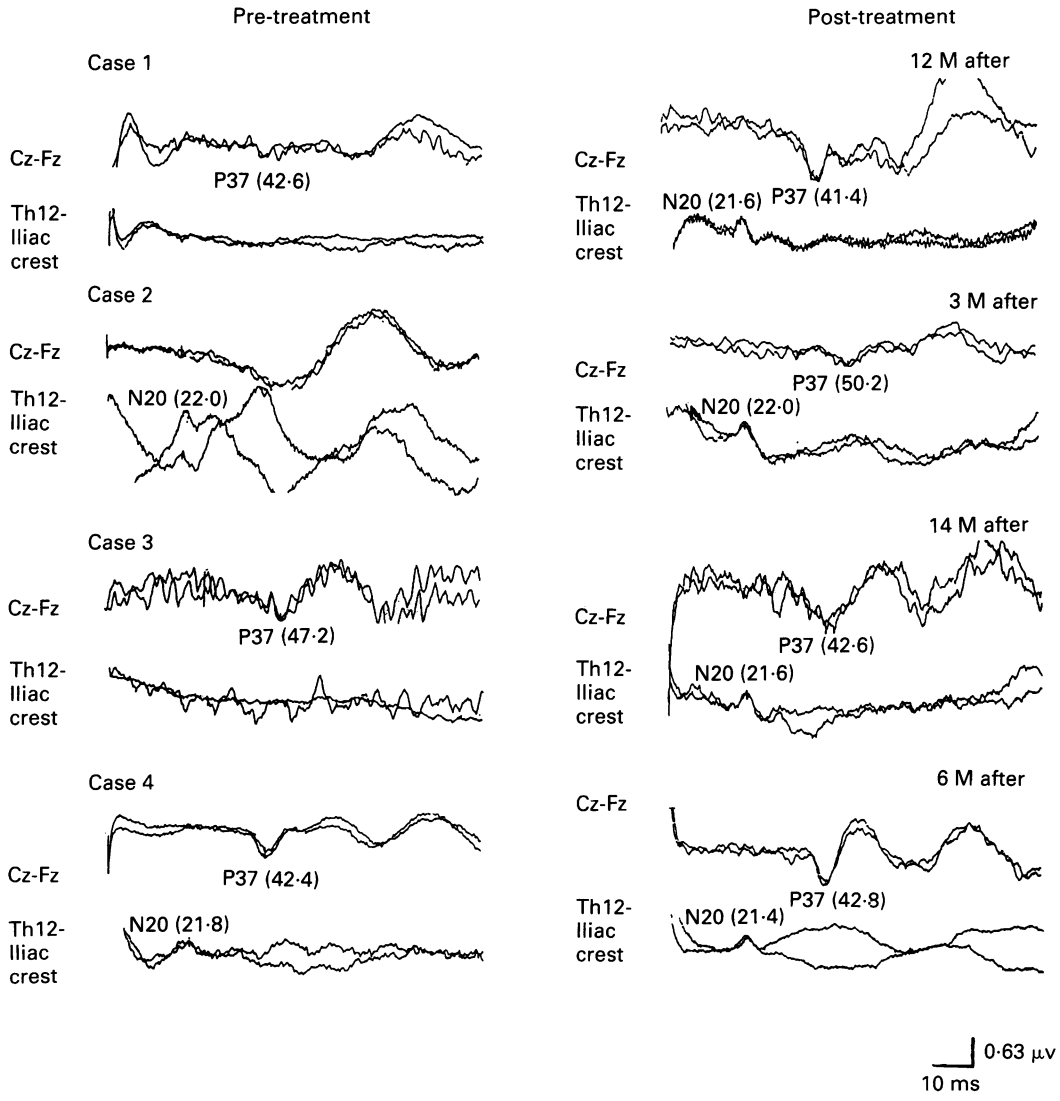

Figure 2 SSEPs obtained from four patients with HAM before and during vitamin C therapy. In cases 1 and 3, peak latency of N20 was not recorded before therapy, but it appeared afterwards; the prolonged peak latency of P37 improved after the therapy. In cases 2 and 4, prolongation of peak latency of N20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

Table Immunological parameters of seven HAM patients before and after vitamin C therapy

Case	Age /sex	Follow up (months)	Serum anti-HTLV titres		CSF anti-HTLV titres		CSF IgG index		Serum IAP (μg/ml)		OKT4/OKT8 in blood	
			Before	After	Before	After	Before	After	Before	After	Before	After
1	51/M	10	4096	4096	32	32	0·71	0·50	1110	403	4·99	5·09
2	60/M	4	20480	40960	512	256	1·29	0·81	380	315	3·00	2·90
3	81/M	2	10240	10240	256	256	1·20	0·60	975	462	1·80	1·30
4	68/M	4	20480	40960	256	256	3·20	1·76	NA	NA	NA	NA
5	36/F	8	20480	20480	256	256	3·50	0·60	468	309	3·00	3·20
6	63/F	3	2048	2048	NA	NA	NA	NA	NA	NA	NA	NA
7	65/F	2	40960	40960	1024	1024	1·28	1·02	800	502	2·34	2·50
Mean	61	4·85	16969	22820	389	347	1·86	0·88	747	398	3·03	3·00
SD	14	3·0	13204	17949	346	344	1·18	0·47	316	86	1·21	1·37
P Value			NS		NS		<0·1		<0·05		NS	

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

relationship with neurological symptoms in all patients. Interestingly, serum IAP levels in two patients (cases 1 and 3 in table) were correlated with disease severity; in case 1, the MMT score and the serum IAP level immediately before on-off study was 1·0 and 310 μg/ml, respectively. During the 2 week period when vitamin C therapy was withdrawn, the MMT score worsened to 6·0, and the serum IAP level increased to 510 μg/ml. Two weeks after restarting vitamin C, the MMT score improved again to 2·0, and the serum IAP level decreased to 413 μg/ml. In case 3, the MMT score worsened from 3·0 to 15 and the serum IAP level increased from 293 μg/ml to 720 μg/ml after two weeks of discontinuation of vitamin C therapy. Two weeks after readministration of vitamin C, the MMT score improved to 10 and the serum IAP level decreased to 480 μg/ml.

During follow up, two patients stopped taking vitamin C, one because of complicating adult T cell leukaemia (three months after start of therapy) and another because of complicating nephrotic syndrome (six months after start of therapy). No serious adverse effects occurred after the therapy.

Discussion

Immunological abnormalities in patients with HAM have been disclosed by several investigators.[1 4-6] A favourable response of HAM patients to immunomodulatory therapeutics has been reported,[6 10] 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,[11 12] 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,[1 7] 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.[8] 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.[9] 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.[5] 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.[5] 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.[13 14] 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.[1] Recently, a sensitive method for determining the level of intrathecal IAP has been developed.[15] 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.[16] 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.[1] 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.

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