High-Dose Vitamin C Therapy for Inclusion Body Myositis

YAMADA, Takeshi
Department of Neurology, Neurological Institute, Graduate School of Medical Sciences, Kyushu University

MINOHARA, Motozumi
Department of Neurology, Neurological Institute, Graduate School of Medical Sciences, Kyushu University

IMAISO, Yasuyuki
Department of Neurology, Neurological Institute, Graduate School of Medical Sciences, Kyushu University

SAKAE, Nobutaka
Department of Neurology, Neurological Institute, Graduate School of Medical Sciences, Kyushu University

他

https://doi.org/10.15017/7218233

出版情報：福岡醫學雜誌. 92 (4), pp.99-104, 2001-04-25. Fukuoka Medical Association
バージョン：
権利関係：

High-Dose Vitamin C Therapy for Inclusion Body Myositis

Takeshi YAMADA[1], Motozumi MINOHARA[1], Yasuyuki IMAISO[1], Nobutaka SAKAE[1], Hideo HARA[1], Kimihiro TANAKA[1], Tatsunori YAMAMOTO[2], Takayuki TANIWAKI[1], Hirokazu FURUYA[1] and Jun-ichi KIRA[1]

[1]*Department of Neurology, Neurological Institute, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan*

[2]*Department of Neurology, University of Occupational and Environmental Health, Kitakyushu 807-8555, Japan*

Abstract Objectives : The efficiency of high-dose vitamin C therapy for inclusion body myositis (IBM) was assessed. Subjects & Methods : The subjects were five patients with IBM confirmed pathologically. After the intravenous administration of 40 mg/kg vitamin C five times/week for four weeks, muscle weakness was found to improve in three cases. The average muscle score improved from 8.1 to 8.8, from 7.0 to 8.1 and from 6.2 to 6.8. Magnetic resonance imaging (MRI) demonstrated a reduction in the size of T2 high lesions and gadolinium enhancement in the thigh muscles in one case. Based on our findings, high-dose vitamin C therapy is considered to be effective in some cases of IBM.

Key words : inclusion body myositis, vitamin C, amyloid, human T-lymphotropic virus type I, HTLV-I

Introduction

Inclusion body myositis (IBM) is classified as one of type of inflammatory myopathy and is pathologically characterized by an infiltration of lymphocytes and nuclear and/or cytoplasmic inclusion bodies containing amyloid fibrils[7]. In contrast to polymyositis/dermatomyositis, IBM is resistant to conventional immunosuppressive therapy, which thus suggests IBM to be a degenerative disease.

All correspondence should be addressed to : Dr. Takeshi Yamada, Department of Neurology, Neurological Institute, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan

Although the etiology of IBM is unclear, a viral infection has been implicated. IBM in human immunodeficiency virus type I (HIV-I) and human T-lymphotropic virus type I (HTLV-I) infected patients has been reported[5]. A persistent retroviral infection may trigger an endomysial inflammatory response. In a previous report, high-dose vitamin C therapy was shown to be effective in the treatment of HTLV-I associated myelopathy/tropical spastic paraparesis (HAM/TSP)[9]. We thus attempted to perform this therapy on cases of IBM with and without HTLV-I infection.

Subjects and methods

Patients

Five patients (two males and three females) fulfilling the diagnostic criteria for IBM[7] were enrolled in this study (Table 1). The mean age

Table 1 response of IBM patients to high-dose vitamin C therapy

case	sex/age	duration (y)	HTLV-I antibody	AMS		CK (U/L)		CD4 (%)		CD8 (%)	
				pre	post	pre	post	pre	post	pre	post
1	62/M	5	+	8.1	8.8	264	394	40.5	41.5	27.8	21.5
2	66/F	4	−	7.0	8.1	174	268	43.8	25.3	14.6	12.5
3	74/F	5	−	7.3	7.4	273	516	41.4	32.8	28.9	31.9
4	77/M	4	−	6.2	6.8	357	495	n.e.	37.5	n.e.	17.4
5	62/F	3	+	8.0	8.1	463	444	57.8	n.e.	34.3	n.e.

AMS, average muscle score. pre, before the therapy ; post , after the therapy. Normal ranges of serum CK : male, 62-287 U/L ; female, 45-163 U/L. Normal ranges of lymphocyte subset percentages : $CD4_+$, 29.1-56.3% ; $CD8_+$, 13.3-35.3%. n.e., not

of onset and the mean duration of illness were 64.0±6.8 (SD) and 4.2±0.8 (SD) years. Muscle weakness was present in the limb muscles including finger flexor and/or quadriceps (Fig. 1). Electromyography (EMG) showed myogenic and/or neurogenic patterns. Serum creatine kinase (CK) was less than four times normal. Pathological studies of biopsied muscles revealed endomysial inflammation, muscle fibers with rimmed vacuoles, and the accumulation of 15 nm tubulofilaments in the sarcoplasm by electron microscopy. None of the cases had a contributory family history. The serum anti-HTLV-I antibody was positive in two cases.

High-dose vitamin C therapy

High-dose vitamin C therapy was performed according to the method of Kataoka et al.[9] with some modifications. A daily dose of 40 mg/kg of vitamin C was intravenously infused five times per week. Muscle strength was assessed by T.Y. using the modified Medical Research Council Scale[3]. The scale was converted to a 0-10 scale as follows : 0=0, 1=1, 2=2, 3−=3, 3=4, 3+=5, 4=7, 5−=9, 5=10. An average muscle score (AMS) of all 34 muscles was determined. The peripheral blood lymphocyte subsets were analyzed by flow cytometry as described previously[8]. Magnetic resonance imaging (MRI) of the lower limb muscles was taken in two cases. These parameters were assessed before and after the treatment for four weeks.

Results

After the treatment, three cases showed an improvement in the muscle scores, but two cases did not, irrespective of HTLV-I infection (Fig. 1). Case 1 showed increases of muscle strength in upper limbs. He could perform five push-ups before the treatment and 20 times after it. Case 2 showed a remarkable improvement in the weakness of the flexor digitorum superficialis and could flex her proximal interphalangeal joints. Her grasp power increased from 0 to 6 kg. Case 4 showed a moderate improvement in the weakness of her wrist flexor and psoas muscles. The AMSs were increased from 8.1 to 8.8 in case 1, from 7.0 to 8.1 in case 2 and from 6.2 to 6.8 in case 4 (Table 1). The mean ± SD of AMS in five patients were 7.3±0.8 and 7.8±0.8 before and after the treatment. The sample size was too small to detect any significant difference ($p=0.053$, t-test). The serum CK levels increased in all cases. The CD4+ T cell percentages decreased in cases 2 and 3. MRI demonstrated a reduction in the T2-high lesions and Gd enhancement in case 1 (Fig. 2) but there were no changes in case 2.

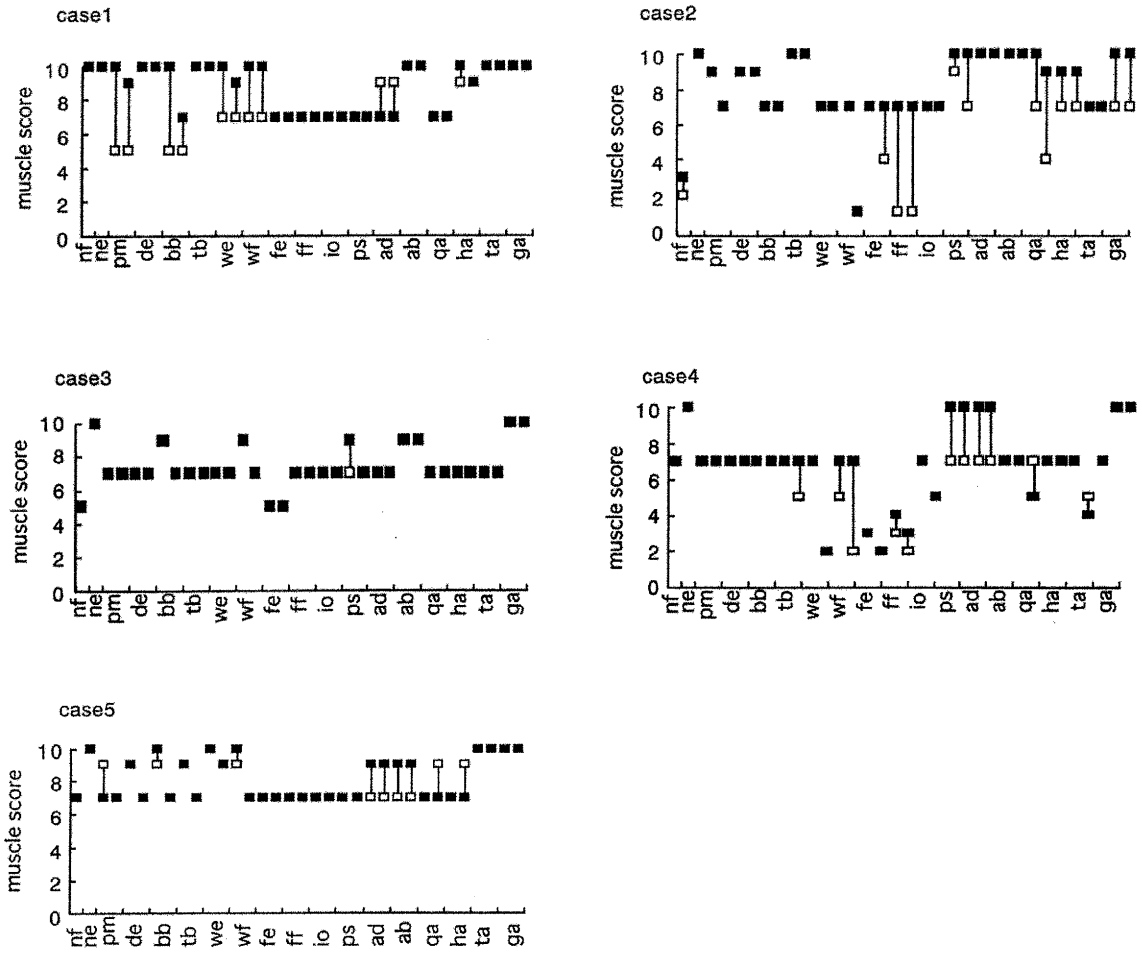

Fig. 1 Differences in muscle scores for ecah muscle. Open square, a muscle score before the treatment; closed square, a muscle score after the treatment. Only the latters are shown when overlapped. Nf, neck flexor; ne, neck extensor; pm, pectoralis major; de, deltoid; bb, biceps brachialis; tb, triceps brachialis; we, wrist extensor; wf, wrist flexor; fe, finger extensor; ff, finger flexor; io, interossei; ps, iliopsoas; ad, thigh adductor; ab, thigh abductor; qa, quadriceps femoris; ha, hamstrings; ta, tibialis anterior; ga, gastrocnemius. The right and left muscles are arranged in order except neck flexor and extensor.

Discussion

There is no established treatment for IBM. Intravenous immunoglobulin (IVIg) has been previously examined as a potential therapy. A double-blind, placebo-controlled study indicated that IVIg did not statistically improve the muscle strength and disability scores on the whole but did significantly improve the muscle strength in the lower limbs and swallowing function[6]. It remains unclear whether IVIg is a valid therapy justifying its high cost.

High-dose vitamin C therapy was found to be effective for three among the five cases of IBM in this study, although our results are not conclusive because it was an open trial with a small

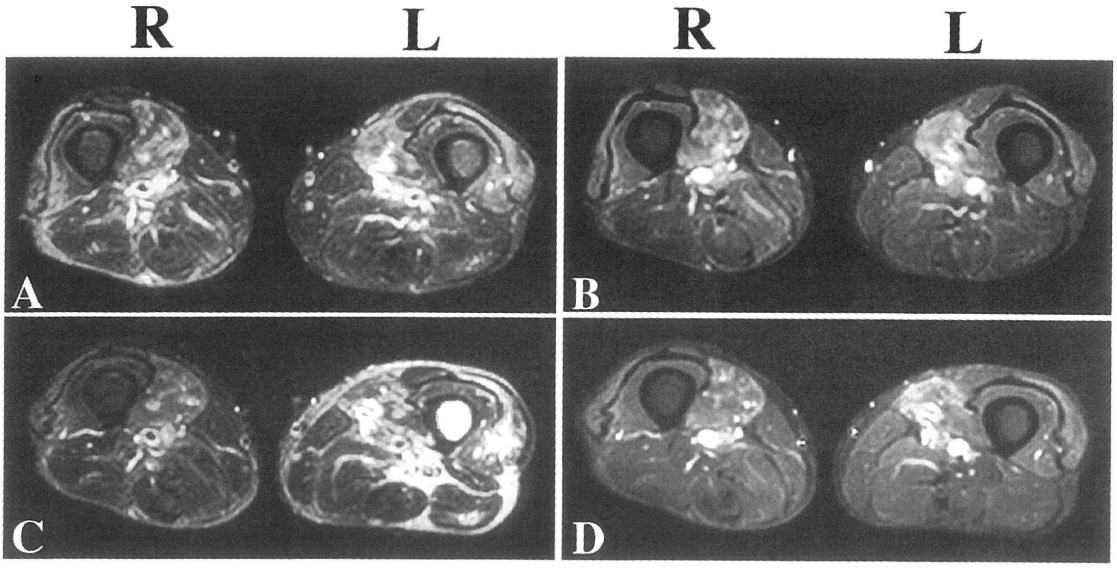

Fig. 2 MRI of the thigh muscles in case 1. High signal lesions of the quadriceps on a T2-weighted image (TR 2600, TE 102) (A) and the gadolinium enhancement on a T1-weighted image (TR 533, TE 11) (B) are reduced markedly on the right side and mildly on the left side after the treatment (C, D).

number of subjects. The serum CK levels increased in the improved cases as well. The elevation was, however, small and may be associated with an increase in the behavioral activity after an improvement of muscle strength.

Kataoka et al.[9] considered the immunomodulatory action of high-dose of vitamin C in the therapy for HAM/TSP. Based on the findings of a decrease in the serum immunosuppressive acidic protein (IAP), which is mainly produced by macrophages, vitamin C suppresses a macrophage activity. In our study, the serum IAP remained normal before and after the treatment although it was sequentially measured in only case 1. Peripheral lymphocyte subset analyses revealed a decrease in the proportion of CD4+ cells in three cases after this treatment, thus suggesting the immunomodulatory action of high-dose vitamin C to affect the response to this treatment.

One of the pathological hallmarks of IBM is amyloid deposition in the muscle fibers as seen in the brains of patients with Alzheimer's disease (AD). This amyloid contains β-amyloid, β-amyloid precursor protein (APP), ubquitin, prion protein, phosphorylated tau protein, apolipoprotein E and acetylcholine receptor protein. In AD, amyloid deposition plays a critical role in the pathophysiology. Amyloid deposition may cause muscle fiber degeneration in IBM although its mechanisms remain unknown. An overexpression of APP in cultured normal human muscle fibers using adenovirus vector induced such pathological aspects of IBM as β-amyloid deposition and tubulofilamentous inclusions[1], which supports a hypothesis that amyloid deposition causes muscle fiber degeneration in IBM. The cytotoxic mechanisms of β-amyloid have been vigorlously investigated. β-amyloid-associated free radicals generate oxidative stress[4], and IBM may be a disease related to oxidative stress[2]. Vitamin C is a radical scavenger[10] and may display a

therapeutic effect by suppressing the oxidative muscle injury of amyloid deposition in IBM.

Vitamin C is a safe and inexpensive drug, and worth administering to IBM patients, although further studies are still called for before any conclusions can be made.

References

1) Askanas V, McFerrin J, Alvarez RB, Baqué S and Engel WK: βAPP gene transfer into cultured human muscle induces inclusion-body myositis aspects. Neuroreport 8: 2155-2158, 1997.

2) Askanas V and Engel WK: Sporadic inclusion-body myositis and hereditary inclusion-body myopathies. Arch Neurol 55: 915-920, 1998.

3) Brooke MH, Fenichel GM, Griggs RC, Mendell JR, Moxley R, Miller JP, Province MA and the CIDD GROUP: Clinical investigation in Duchenne dystrophy: 2. Determination of the "power" of therapeutic trials based on the natural history. Muscle & Nerve 6: 91-103, 1983.

4) Butterfield DA: β-amyloid-associated free radical oxidative stress and neurotoxicity: implications for Alzheimer's disease. Chem Res Toxicol 10: 495-506, 1997.

5) Cupler EJ, Leon-Monzon M, Miller J, Semino-Mora C, Anderson TL and Dalakas MC: Inclusion body myositis in HIV-1 and HTLV-1 infected patients. Brain 119: 1887-1893, 1996.

6) Dalakas MC, Sonies B, Dambrosia J, Sekul E, Cupler E and Sivakumar K: Treatment of inclusion-body myositis with IVIg: a double-blind, placebo-controlled study. Neurology 48: 712-716, 1997.

7) Griggs RC, Askanas V, Dimauro S, Engel A, Karpati G, Mendell JR and Rowland LP: Inclusion body myositis and myopathies. Ann Neurol 38: 705-713, 1995.

8) Itoyama Y, Kira J, Fujii N, Goto I and Yamamoto N: Increases in helper inducer T cells and activated T cells in HTLV-I-associated myelopathy. Ann Neurol 26: 257-262, 1989.

9) Kataoka A, Imai H, Inayoshi S and Tsuda T: Intermittent high-dose vitamin C therapy in patients with HTLV-I associated myelopathy. J Neurol Neurosurg Psychiatry 56: 1213-1216, 1993.

10) Rose RC and Bode AM: Biology of free radical scavengers: an evaluation of ascorbate. FASEB J 7: 1135-1142, 1993.

(Received for publication March 1, 2001)

(和文抄録)

封入体筋炎に対するビタミンC大量療法

[1]九州大学大学院医学研究院脳神経病研究施設神経内科
[2]産業医科大学神経内科
山田　猛[1]・三野原元澄[1]・今磯泰幸[1]
栄　信孝[1]・原　英夫[1]・田中公裕[1]
山本辰紀[2]・谷脇考恭[1]・古谷博和[1]
吉良潤一[1]

目的：封入体筋炎に対するビタミンC大量療法の効果を調べた．対象と方法：対象は病理学的に確認された封入体筋炎患者5例．体重kgあたり40 mgのビタミンC静脈内投与を週5回4週間行ったところ，3例で筋力低下の改善がみられた．平均筋力スコアが8.1から8.8，7.0から8.1，6.2から6.8に改善した．1例のMRI検査で大腿筋群のT2延長病変の大きさとガドリニウム増強効果の減少が認められた．これらの効果から，ビタミンC大量療法は封入体筋炎の症例に有効な場合があると考えられた．