Hiroshima J. Med. Sci.
Vol. 55, No. 1, 35~37, March, 2006
HIJM 55–5

Efficacy of Neurotropin in Chronic Fatigue Syndrome: a Case Report

Katsuhiro TODA[1, *)] and Hiroaki KIMURA[2)]

1) Department of Rehabilitation, Hiroshima Prefectural Rehabilitation Center, 295–3 Taguchi, Saijyou-chou, Higashi-Hiroshima, Hiroshima 739–0036 Japan

2) Department of Rehabilitation, Hiroshima University Hospital, 1–2–3 Kasumi, Minami-ku, Hiroshima 734–8551 Japan

ABSTRACT

Chronic fatigue syndrome (CFS) is a disorder that causes general fatigue and chronic widespread pain. A 28-year-old male visited an outpatient department due to general fatigue and pain involving the entire body. He did not suffer from fibromyalgia, but he was diagnosed with CFS. At the initial visit, he complained of lack of concentration, memory decline, frequent urination, insomnia and occasional difficulty of emotional control, as well as general fatigue and pain involving the entire body. Four tablets of Neurotropin per day alone were administered. General fatigue and pain were gradually alleviated one week later. His sleep condition, concentration power, and memory also improved two weeks later. Medication was discontinued from 11 weeks based on the patient's judgment as he felt little general fatigue and pain involving the entire body. Treatment was completed 3 months later. The symptoms disappeared and did not recur five months after the discontinuation of Neurotropin. He was looking for a job without fatigue and pain 8 months later (5 months after the cessation of treatment). The functional mechanisms of Neurotropin in CFS are unknown.

Key words: *Chronic fatigue syndrome, Fibromyalgia, Neurotropin*

Chronic fatigue syndrome (CFS) is a disorder which causes general fatigue, chronic widespread pain, malaise, impaired memory and concentration, etc[1,10,11]. Neurotropin (NT; Nippon Zoki Pharmaceutical Co., Ltd., Osaka, Japan) has been widely used to treat chronic pain in Japan. We present a CFS patient who responded to NT. This is the first report which shows the efficacy of NT in CFS.

CASE REPORT

A 28-year-old male visited an outpatient department due to general fatigue and pain involving the entire body. He had usually slept three hours a night. General fatigue had occurred in 2001 and his symptoms had gradually deteriorated. He had felt pain involving the entire body for 3 years. He visited several hospitals and was diagnosed with depression and/or overwork. He returned to his parents' home in August 2003, because he could not perform his job. At his initial visit, he complained of lack of concentration, memory decline, frequent urination, insomnia and occasional difficulty of emotional control as well as general fatigue and pain involving the entire body. Laboratory tests including urinalysis at the initial visit showed no abnormalities, except slightly elevated ALP. Physical examination revealed a slightly increased symmetric tendon reflex. Brain MRI and cervical MRI showed no abnormalities. He did not satisfy the diagnostic criteria of fibromyalgia established by the American College of Rheumatology[14] because only two tender points were positive. He satisfied the US Center for Disease Control and Prevention (CDC) clinical definition for CFS[3]. CFS, a physical disorder, accounted for the symptoms; therefore, somatoform disorders were excluded. His performance status[5] was 7 (unable to carry on normal activity or to do light task at all; able to care for self without assistance). Four tablets of NT per day alone were administered. General fatigue and pain involving the entire body were gradually alleviated over one week. His sleep condition, concentration power, and memory had also improved two weeks later. Medication was discontinued from 11 weeks based on the patient's judgment as he felt

* Address for reprints: Katsuhiro Toda, M.D., Ph.D., Department of Rehabilitation, Hiroshima Prefectural Rehabilitation Center, 295–3 Taguchi, Saijyou-chou, Higashi-Hiroshima, Hiroshima 739–0036 Japan
Fax: +81–82–425–1094, Tel: +81–82–425–1455

little general fatigue and pain involving the entire body. Treatment was completed 3 months later because he lived far from our hospital. His performance status improved to 1 (able to carry on normal activity, but sometimes feels fatigue). General fatigue and pain involving the entire body dropped to approximately 5% compared with that before consultation. He was seeking employment without fatigue and pain 8 months later (5 months after the cessation of treatment).

DISCUSSION

NT, a non-protein extract from the inflamed skin of rabbits inoculated with vaccinia virus, is thought to cause the activation of a descending pain inhibitory system[12]. NT has been widely used in Japan to treat chronic pain. A double-blind cross-over study for complex regional pain syndrome is underway at the National Institutes of Health (protocol number: 00-D-0200). NT is an analgesic, but it does not suppress the synthesis of prostaglandin. In rats, NT even decreases nonsteroidal antiinflammatory drug (NSAID) ulcers[4] and prevents some kinds of stress ulcers[15]. Adverse effects of NT are few and slight.

CFS is a medically unexplained disorder that causes persistent or relapsing fatigue lasting 6 months or longer[2,9]. The onset of CFS is typically sudden, often associated with an upper respiratory infection or a flu-like illness[2]. CSF is often associated with fibromyalgia[1,13]. The CDC clinical definition for CFS[3] is the most common diagnostic criterion for CFS. According to the CDC clinical definition for CFS[3], the following conditions exclude a patient from the diagnosis of CFS. CFS is excluded if another cause for CFS is found: 1. Any active medical condition that may explain the presence of chronic fatigue. 2. Any previously diagnosed medical condition whose resolution has not been documented beyond reasonable clinical doubt and whose continued activity may explain the chronic fatigue illness. 3. Any past or current diagnosis of a major depressive disorder. 4. Alcohol or other substance. 5. Severe obesity. According to the CDC clinical definition for CFS[3], the following conditions do not exclude a patient from the diagnosis of CFS: 1. Fibromyalgia, anxiety disorders, somatoform disorders, nonpsychotic or nonmelancholic depression, neurasthenia, and multiple chemical sensitivity disorders. 2. Any condition under specific treatment sufficient to alleviate all symptoms related to that condition and for which the adequacy of treatment has been documented. 3. Any condition, such as Lyme disease or syphilis, that was treated with definitive therapy before development by pulmonary function and other testing. 4. Any isolated and unexplained physical examination finding or laboratory or imaging test abnormality that is insufficient to strongly suggest the existence of an exclusionary condition.

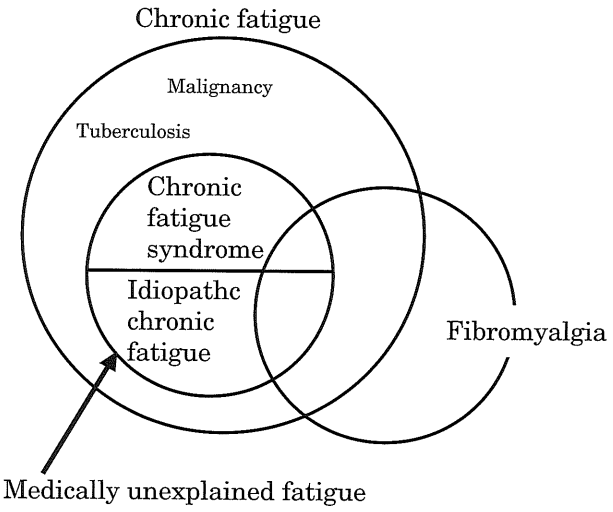

Fig. 1. Relationships among chronic fatigue, chronic fatigue syndrome, idiopathic chronic fatigue, medically unexplained fatigue, and fibromyalgia.
Chronic fatigue is defined as self-reported persistent or relapsing fatigue lasting 6 months or longer. Medically unexplained fatigue includes chronic fatigue syndrome and idiopathic chronic fatigue. Idiopathic chronic fatigue is defined as a medically unexplained fatigue that fails to meet the criteria for chronic fatigue syndrome. Chronic fatigue syndrome is defined as a medically unexplained fatigue that meets the criteria for chronic fatigue syndrome.

Medication that is effective for fibromyalgia is often effective for CFS. Because NT is effective for fibromyalgia[7,8] and its adverse effects are few and slight, we used NT as a first-line treatment for CFS. As mentioned above, NT is effective for chronic pain and its analgesic mechanisms are thought to involve the activation of a descending pain inhibitory system[12]. However, the mechanisms cannot explain the efficacy of NT for CFS. The function mechanisms of NT in CFS are unknown. NT activates an immunological function[6]. We speculate that the activation of an immunological function inhibits the virus, resulting in the resolution of CFS. NT is a non-protein extract from the inflamed skin of rabbits inoculated with vaccinia virus and a viral infection theory is one of the major etiologies of CFS. These factors support this hypothesis.

We present a CFS patient who responded to NT. However, further studies are needed to confirm the efficacy of NT for CFS.

(Received November 15, 2005)
(Accepted January 10, 2006)

REFERENCES

1. **Afari, N. and Buchwald, D.** 2003. Chronic fatigue syndrome: a review. Am. J. Psychiatry **160:** 221–236.
2. **Fan, P.T.** 2004. Fibromyalgia and chronic fatigue syndrome. APLAR Journal of Rheumatology **7:** 219–231.
3. **Fukuda, K., Straus, S.E., Hickie, I., Sharpe, M.C., Dobbins, J.G. and Komaroff, A.** 1994. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann. Intern. Med. **121:** 953–959.
4. **Higashiguchi, T., Go, K. and Yoneda, R.** 1987. Combined effects of the extract from rabbit skin tissues inoculated with vaccinia virus (neurotropin) with non-steroidal acidic anti-inflammatory drugs. Jpn. Pharmacol. Ther. **15:** 255–266. (abstract in English)
5. **Kuratsune, H., Yamaguti, M., Takahashi, S., Tagawa, T., Machii, T. and Kitani, T.** 1995. Abnormal cellular carnitine metabolism in chronic fatigue syndrome. J. Immunol. Immunopharmacol. **15:** 41–44.
6. **Nagano, K., Sugisaki, T., Taguchi, K., Hara, T., Naiki, M. and Mori, H.** 2003. A murine model of enterohemorrhagic Escherichia coli O157:H7 infection to assess immunopotentiating activity of drugs on mucosal immunity: effect of drugs. J. Pharmacol. Sci. **91:** 219–228.
7. **Nagaoka, S., Nakamura, M. and Sekiguchi, A.** 2004. An open clinical trial of neurotropin in patients with fibromyalgia. Rheumatology **32:** 104–108. (abstract in English)
8. **Nishioka, M., Akimoto, M., Usui, C., Ishizuka, T., Arai, H., Nakamura, H. and Nishioka, K.** 2004. Clinical condition and conception of fibromyalgia. Japan Medical Journal **4177:** 10–14. (in Japanese)
9. **Ranjith, G.** 2005. Epidemiology of chronic fatigue syndrome. Occup. Med. (Lond) **55:** 13–19.
10. **Reid, S., Chalder, T., Cleare, A., Hotopf, M. and Wessely, S.** 2004. Chronic fatigue syndrome. Clin. Evid. 1578–1593.
11. **Rimes, K.A. and Chalder, T.** 2005. Treatments for chronic fatigue syndrome. Occup. Med. (Lond) **55:** 32–39.
12. **Toda, K., Muneshige, H. and Ikuta, Y.** 1998. Antinociceptive effects of neurotropin in a rat model of painful peripheral mononeuropathy. Life Sci. **62:** 913–921.
13. **White, K.P., Speechley, M., Harth, M. and Ostbye, T.** 2000. Co-existence of chronic fatigue syndrome with fibromyalgia syndrome in the general population. A controlled study. Scand. J. Rheumatol. **29:** 44–51.
14. **Wolfe, F., Smythe, H.A., Yunus, M.B., Bennett, R.M., Bombardier, C., Goldenberg, D.L., Tugwell, P., Campbell, S.M., Abeles, M., Clark, P., Fam, A.G., Farber, S.J., Fiechtner, J.J., Franklin, C.R., Gatter, R.A., Hamaty, D., Lessard, J., Lichtbroun, A.S., Masi, A.T., McCain, G.A., Reynolds, J., Romano, T.J., Russell, I.J. and Sheon, R.P.** 1990. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum. **33:** 160–172.
15. **Yoneda, R., Oshima, K., Inoue, A., Mikami, H., Ohara, H., Kawamura, M., Sugahara, K., Go, K. and Hata, T.** 1981. Preventive effect of extract isolated from vaccnia virus inoculated and inflamed skin of rabbit (neurotropin) on experimental acute ulcer. Oyo Yakuri **21:** 595–605. (abstract in English)