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The Effect of Bovine Brain Gangliosides on Essential Tremor

Fumiko ISHIZAKI[1], Toshihide HARADA[2], Shozo KITO[3], Akira HARADA[1], Masayumi SAEKI[4] and Shigenobu NAKAMURA[1]

1) Third Department of Internal Medicine, Hiroshima University School of Medicine, Hiroshima
2) Hiroshima Prefectural Hospital, Hiroshima
3) Division of Health Sciences University of the Air, Chiba
4) First Department of Internal Medicine, Hiroshima University School of Medicine, Hiroshima

ABSTRACT

We reported the case of a 74-year-old woman suffering from essential tremor for 20 years which was treated effectively with purified bovine brain gangliosides containing GM1, GD1a, GD1b and GT1b gangliosides. The trials of the treatment were conducted twice, 40 mg and 20 mg gangliosides per day respectively administered intramuscularly. Essential tremor dramatically improved with gangliosides on the second day of treatment, suggesting that the effect of gangliosides was not induced by neuronal sprouting or regeneration. It is speculated that a certain type of essential tremor is a reversible disease of membrane disorder.

Key words: *Gangliosides, Essential tremor, Therapeutic trials, Diabetic neuropathy*

Gangliosides are a series of complex acidic glycolipids that are concentrated in cell membranes, particularly in neuron[17]. Exogenously administered gangliosides have been reported to promote nerve regeneration[8,10]. In most cases, this has been hypothesized to be due to stimulation of neuronal growth or sprouting[6,11,16]. It is reported that purified bovine brain gangliosides have a beneficial effect on degenerative disease and diabetic neuropathy[1,2,7,15].

Essential tremor is a chronic, slowly progressive neurological disease[4,9,14], manifesting as action and postural tremor in the upper extremities and less frequently in the head and other parts of the body. However, the pathophysiology of essential tremor is not clear and the treatment is often unsatisfactory.

We report a case of essential tremor for which gangliosides were effective.

CASE REPORT

A 74-year-old woman, height: 159.4 cm, weight: 61 kg, no family history of tremor, developed bilateral tremulous hands at the age of 54 years. Later, her head and legs also became affected. She was affected by mild diabetes mellitus for about 13 years, and recently this was accompanied with retinopathy, Scott IIIa, and peripheral neuropathy. In August 1985, the patient was admitted to Hiroshima University Hospital for treatment of diabetic neuropathy with gangliosides. Neurological examination revealed a constant titubation of the head and static tremor of both hands and legs, especially the right, grossly increased by volitional activity with an intention element. Tremor was absent at rest. Her handwriting was affected by the tremor and influenced by emotional factors, but there was no micrographia. Her speech was also tremulous. The frequency of the hand tremor was 5 Hz (Fig. 1). She had neither a mask-like expression nor rigid neck or arms, but her legs were rigid. She was unsteady on gait, but showed no cerebellar signs. Both plantar response were flexor in type. She had glove-stocking type sensory disturbance, and vibration sense was also disturbed in the distal extremities. She had had a long history of

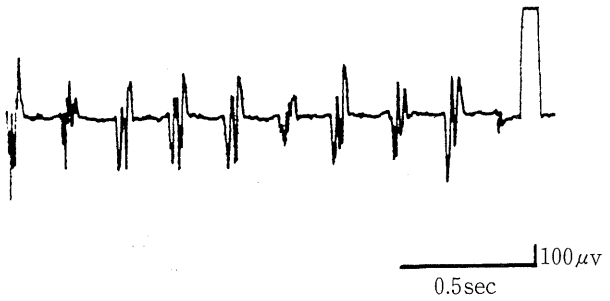

Fig. 1. Surface electromyogram of hand tremor. Frequency of hand tremor is 5Hz.

Address: Fumiko Ishizaki, MD, Third Department of Internal Medicine, Hiroshima University School of Medicine, Kasumi 1-2-3, Minami-ku, Hiroshima 734, Japan

mild hypertension, but her blood pressure was currently normal. Since 1963, she suffered from lower back pain and gait disturbance. She had several surgical operations on her back for narrow spinal canal and the herniation of nucleus pulposus at the lumbar level in 1965, 1966 and 1978. After the last operation, she became aware of the urinary trouble and the motor and sensory disturbance in the legs.

Routine biochemistry showed an elevated blood sugar and serum cholesterol. Glucose tolerance test showed a diabetic pattern; before: 122 mg/dl, after 30 min: 173 mg/dl, 60 min: 263 mg/dl, 120 min: 288 mg/dl, 180 min: 182 mg/dl. Electrolytes, triglycerides, liver function tests, serological test and protein electrophoresis were normal. Nerve conduction studies showed boderline slowing of motor nerve conduction velocity (MCV) in the right peroneal nerve (35.1 m/sec) and normal MCV in both medial and ulnar-nerves. Gangliosides were available for the treatment of diabetic neuropathy from the Eisai Company. Mixed ganglioside compound contained GM1, GD1a, GD1b, and GT1b gangliosides. The patient gave informed consent for the treatment. She was given gangliosides intramuscularly with 2 trials, 40 mg and 20 mg per day respectively. The duration of each trial was 5 days a week for 4 weeks. Unexpectedly her tremor almost disappeared on the day after she started taking 40 mg gangliosides. She had exacerbation after the first trial ended. The second trial started 8 weeks after the first trial, and her tremor improved again on the second day of the trial. The therapeutic efficacy of the second trial continued for over 2 weeks after the ganglioside treatment. The response of gangliosides was reduction in the amplitude of tremor but with no change in frequency. The hand and arm tremor showed the greatest response. Fig. 2 shows samples of her signature and an Archimedes circle which she drew before and after treatment. Therapeutic efficacy on peripheral neuropathy, however, was not demonstrated. Biochemical test and MCV in the peripheral nerves were not significantly altered by the treatment.

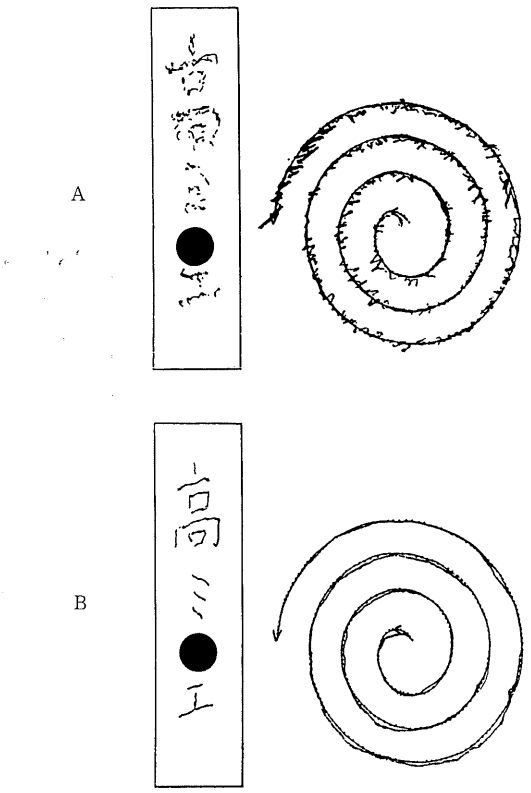

Fig. 2. Therapeutic efficacy of gangliosides on the patient's signature and an Archimedes circle. A: Dec. 12, 1985, before treatment. B: Dec. 16, 1985, four days after treatment of the second trial with 20 mg gangliosides per day.

DISCUSSION

There have been reports of the effect of purified bovine brain gangliosides in uncontrolled and controlled therapeutic trials in human diabetic neuropathy[1,15]. Although the original purpose of using gangliosides in our case was the treatment of diabetic polyneuropathy, the therapeutic efficacy was not shown on peripheral neuropathy. Essential tremor from which the patient had suffered for many years unexpectedly and dramatically improved with gangliosides. The therapeutic efficacy of gangliosides on essential tremor has not been reported. Essential tremor is no longer considered to be a homogeneous disorder. Marsden et al[14] have proposed 4 subclasses of essential tremor that differ in their manifestation and possibly pathogenesis. Type 1 is benign exaggerated physiological essential tremor. Type 2 is benign pathological essential tremor. Type 3 is severe pathological essential tremor. Type 4 is symptomatic essential tremor associated with other neurological conditions such as peripheral neuropathy, torsion dystonia, and Parkinson's disease. We classified our patient as to type 2. Although she had peripheral neuropathy, the history of essential tremor started before the onset of peripheral neuropathy. Also, the signs and symptoms of neuropathy were not changed with gangliosides.

Pathophysiology of essential tremor is still uncertain. If the active site of gangliosides is made clear, the mechanism of some types of essential tremor could be elucidated. Gangliosides had been reported to play an important role in stimulation of neuronal growth or sprouting[6,11,16]. In the case presented here, therapeutic effect of gangliosides on essential tremor appeared from 24 to 48 hours after the treatment. These effects of gangliosides cannot be attributed to increasing sprouting, especially within such a short time frame. Several of the CNS studies[5,8] indicated that gangliosides might have a short-term effect on the CNS after injury. This could not be explained by facilitated sprouting/regeneration. Ganglioside incorporation

into synaptic membrane seemed to activate enzymes, such as (Na, K) adenosine triphosphatase, adenylcyclase, phosphodiesterase, causing functional changes in these membrane activities and stimulating sprouting[5,12,13]. If the therapeutic efficacy of gangliosides could be ascribed to the activation of membrane enzymes, it is postulated that membrane dysfunction might cause essential tremor. Gangliosides improve essential tremor quickly after treatment despite the long duration of the disease. This suggests that a certain type of essential tremor is a reversible disease of membrane disorder.

In conclusion, gangliosides treatment does seem to have a positive effect on essential tremor. In this case, gangliosides modulated the amplitude of tremor, but not the frequency, suggesting that they were not involved in the rhythm formation of tremor. Further studies are needed to assess the long term efficacy of this group of drugs.

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