Case Report: Thyrotropin-Releasing Hormone-Induced Myoclonus and Tremor in a Patient With Hashimoto's Encephalopathy

KAZUHIRO ISHII, MD, AKITO HAYASHI, MD, AKIRA TAMAOKA, MD, SATOSHI USUKI, MD,* HIDEHIRO MIZUSAWA, MD, SHIN'ICHI SHOJI, MD

ABSTRACT: The authors investigated the possibility of a thyrotropin-releasing hormone-related mechanism in a 43-year-old Japanese woman with Hashimoto's encephalopathy who experienced three relapses closely associated with the menstrual cycle. Her symptoms began at ovulation, worsened during the luteal phase, and improved during the menstruation phase. No abnormalities were found by brain magnetic resonance imaging and cerebral angiography. Intravenous administration of thyrotropin-releasing hormone induced symptoms of myoclonus and tremor similar to those observed during an exacerbation. The intensity and duration of involuntary movements induced by thyrotropin-releasing hormone were dose-dependent. The patient's symptoms were controlled effectively by thyroxine replacement therapy. On the basis of these findings, thyrotropin-releasing hormone may have an important role in Hashimoto's encephalopathy. KEY INDEXING TERMS: Hashimoto's encephalopathy; Relapses; Thyrotropin-releasing hormone (TRH); Menstrual cycle; Thyroxine replacement. [Am J Med Sci 1995;310(5):202–205.]

Encephalopathy associated with Hashimoto's thyroiditis, which is distinct from typical myxedema encephalopathy, is characterized by a subacute onset and a relapsing course associated with confusion, cerebellar ataxia, myoclonus, tremor, and stroke-like episodes.[1,2] The pathogenesis of Hashimoto's encephalopathy has not been established, but an autoimmune-related mechanism[2,3] and an excessive thyrotropin-releasing hormone (TRH) mechanism[4,5] have been proposed. We investigated the possibility of a TRH-related mechanism in a patient with Hashimoto's encephalopathy. To our knowledge, this is the first TRH trial in a patient with this disorder.

Case Report

In April 1992, a 43-year-old Japanese woman began to experience occasional tremors in her arms. Two months later, she experienced a transient loss of consciousness and was admitted to the hospital. She complained of unsteadiness when standing. Findings on admission included action tremor in both hands, myoclonus in all extremities, cerebellar ataxia, and confusion. Herpes simplex encephalitis tentatively was diagnosed, and she was treated with acyclovir, but her symptoms grew worse. On July 31, she experienced a generalized seizure and was transferred to our hospital. Neurologic examination revealed a confusional state, bilateral cerebellar ataxia, myoclonus and tremor in all extremities, and generalized hyperreflexia. By analysis of cerebrospinal fluid (CSF), we found an elevated protein level without pleocytosis. Brain magnetic resonance imaging was normal, and an electroencephalogram (EEG) showed diffuse slowing. Hashimoto's thyroiditis was diagnosed based on a positive thyroid microsome antibody assay and the presence of mild hypothyroidism (thyroid-stimulating hormone [TSH] 49.5 μU/mL, free T4 0.6 ng/mL). Her symptoms improved within several days, and she was discharged on September 3, with a prescription for phenytoin (200 mg daily).

On October 16, she again experienced tremor and myoclonus and was readmitted to the hospital. A general physical examination revealed no evidence of hypothyroidism. Her thyroid gland was not enlarged or tender, and had a smooth surface. Neurologic examination showed a confusional state. Slurred speech and bilateral limb ataxia were evident. Coarse tremors were observed in both hands and myoclonus in the extremities. Symmetrical hyperreflexia and bilateral extensor plantar responses were present. No other neurologic focal signs were detected. Routine hematologic and biochemical blood tests were normal. Levels of serum thyroxine (T_4), triiodothyronine (T_3), free triiodothyronine, and reverse triiodothyronine were normal, but her free T_4 level was decreased (0.57 ng/mL) and her TSH level was increased (21.4 μU/mL). Levels of other hormones were normal. She had a positive thyroid microsome antibody titer (1/6,400), but was negative for other autoantibodies, including anti-thyroglobulin antibody, anti-TSH receptor antibody, anti-T_3 and T_4 antibodies, and anti-nuclear antibody. Immune complex formation was normal. Tests for activated platelet-releasing reactions, including beta-thromboglobin and platelet factor 4, were negative. Analysis of CSF showed a normal cell count but an increased protein content. No significant change in viral titers was detected in serum or CSF. No abnormalities

*From the Departments of Neurology and *Obstetrics and Gynecology, Institute of Clinical Medicine, University of Tsukuba, Japan.*

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Correspondence: Akito Hayashi, MD, Department of Neurology, Institute of Clinical Medicine, University of Tsukuba, Tsukuba-City, Ibaraki-ken 305, Japan.

were detected by brain magnetic resonance imaging during periods of remission or exacerbation. Brain scintigraphy showed no abnormal accumulation of $^{99m}TcO_4^-$. Cerebral angiography (4-vessel arteriogram) showed no vasculitis or stenosis. An EEG showed diffuse slowing, with a sporadic bilateral sharp wave that reached its maximum in the frontal region during an exacerbation but was almost normal during a remission. Evaluation of somatosensory-evoked potentials showed normal findings. Hashimoto's encephalopathy was diagnosed based on these findings. Phasic alterations in gonadotropic and gonadal hormone levels and basal body temperature indicated that the menstrual cycle was normal. A gynecologic examination was normal. Three episodes of remission and exacerbation were observed during four cycles of menstruation (Figure 1). Symptoms started at ovulation, worsened during the luteal phase, and improved during the menstruation phase. The series of serum TSH level was not related to the relapses, and serum and CSF levels of TRH were within normal ranges (normal CSF TRH: 18.2 ± 6.2 pg/mL; normal serum TRH: 10.1 ± 1.5 pg/mL).

Methods. Informed consent was obtained from the patient before initiation of the study. After she had fasted overnight, TRH (Tanabe, Osaka, Japan) was infused for 2 minutes through an indwelling venous catheter inserted in the forearm (0.5 and 2 mg during a remission and an exacerbation). Venous blood samples were obtained at 0, 15, 30, 45, 60, 90, and 120 minutes and assayed for TSH and prolactin. Before and after injection of TRH, the patient's neurologic status was assessed, EEG was performed, and the Token test score, which was a battery for aphasia and simple higher function,[6] were determined. A surface electromyogram (EMG) was recorded in the right pectoris major, deltoid, biceps, and triceps muscles.

Results. The patient experienced transient tremors in the upper extremities and myoclonus in the shoulder girdle 30 seconds after injection of TRH. The surface EMG recording showed a synchronous discharge in each muscle (Figure 2). Myoclonus and tremor lasted approximately 7 minutes after injection of 0.5 mg TRH and 13 minutes after injection of 2 mg TRH. In the right biceps muscle, the 2-mg dose of TRH induced an increase in the mean amplitude of movement compared with the 0.5-mg dose on the surface EMG. Involuntary movement was more severe during an exacerbation than during a remission (Table 1). There were no significant changes on EEG or in the Token test scores before or after TRH injection. Administration of TRH was associated with a hyperactive TSH response, consistent with hypothyroidism. The prolactin response was normal (Figure 3).

During the second relapse, we changed her anticonvulsant to valproate. After the third relapse, she was given 25 μg oral thyroxine once daily to treat her hypothyroidism without steroid therapy. She gradually became euthyroid in response to this treatment regimen, and she has experienced no subsequent relapses.

Discussion

Researchers suggest that autoimmune cerebral vasculitis may be involved in the pathogenesis of Hashimoto's encephalopathy.[1,3] In our case, brain scintigraphy, magnetic resonance imaging, and cerebral arteriography showed little evidence of cerebral vasculitis. Brain et al[2] suggested that there may be an unidentified antibody common to the brain and the thyroid gland. However, Latinville et al[4] reported that changes in serum TSH levels paralleled changes in the clinical status of the patient with Hashimoto's encephalopathy, and speculated that an increase in cerebral TRH may cause symptoms of Hashimoto's encephalopathy. In our patient, the serum TSH level was not correlated with changes in the pattern of symptoms. Estimation of the in vivo cerebral TRH concentration is difficult, and this difficulty may explain why the TRH level in CSF in our patient appeared to be normal.

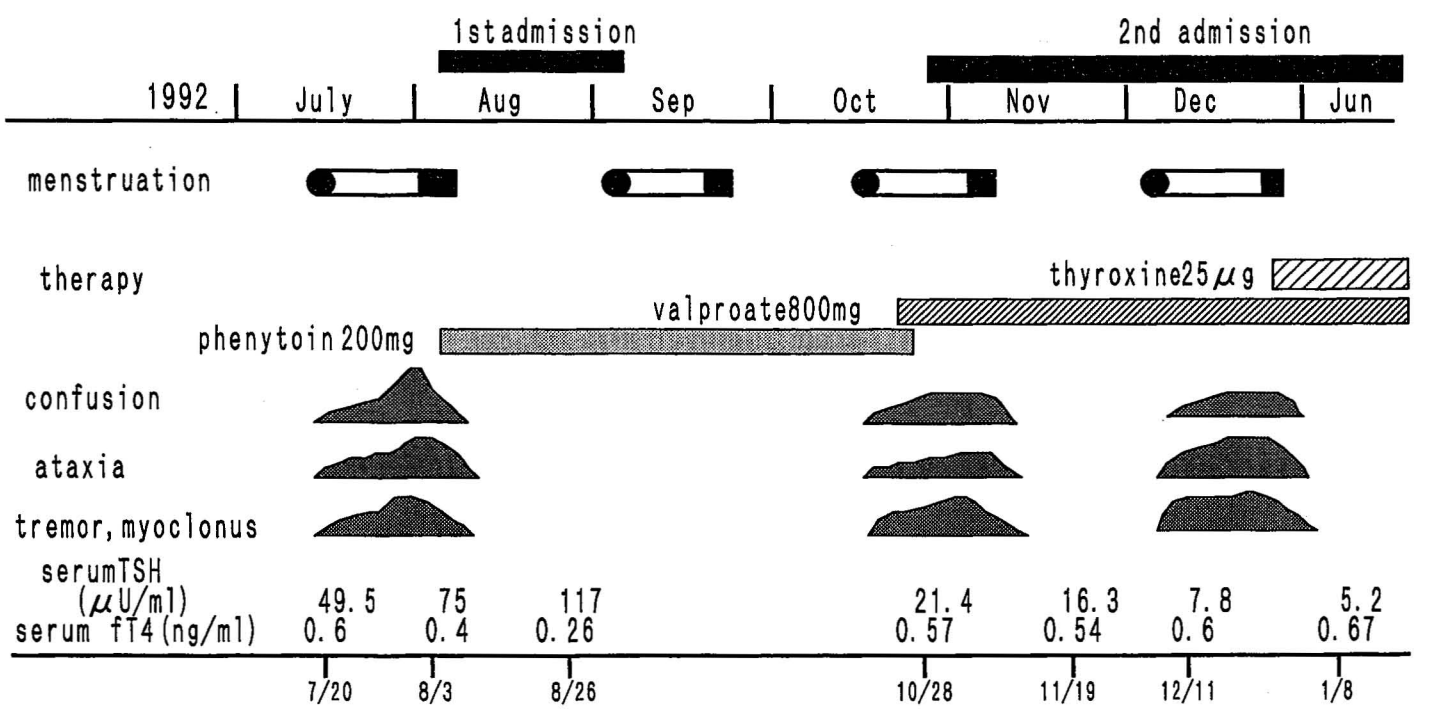

Figure 1. Clinical manifestations and course. fT4: normal range 0.8–2.1 ng/mL; thyroid-stimulating hormone: normal range 0.3–4.0 μU/mL. Note the relation between menstrual cycles and relapses. The relapses were not correlated with thyroid-stimulating hormone and thyrotropin-releasing hormone levels. ● ovulation, □ luteal phase, ■ menstrual phase.

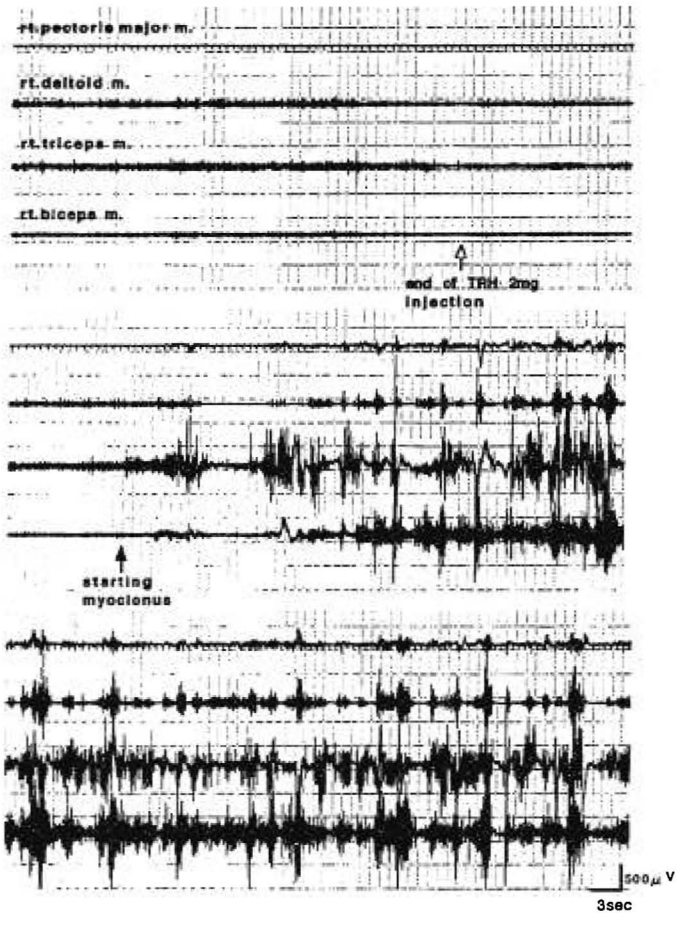

Figure 2. Thyrotropin-releasing hormone stimulation test. White arrowhead indicates an end of 2-mg thyrotropin-releasing hormone injection. Black arrowhead indicates a starting point of the myoclonus. Surface electromyogram recording showing a synchronous discharges in each muscle.

Thyrotropin-releasing hormone induced symptoms of myoclonus and tremor similar to those seen during an exacerbation. The intensity and duration of myoclonus and tremor induced by TRH were dose dependent. Intravenous administration of TRH has caused seizures and involuntary movements in experimental animals[7] and in a patient with epilepsy.[8] Injection of TRH directly into sensitive brain areas in rats produced tremor or shivering.[9] On the basis of these findings, the TRH-induced involuntary movements in our case may have been mediated by the brain. Cerebellar ataxia, a confusional state, and convulsions were not induced by exogenous TRH in the current case. However, it is possible that a higher dose of TRH would have induced these symptoms. Thyrotropin-releasing hormone has had beneficial effects on ataxia in patients with spinocerebellar degeneration,[10] disturbed consciousness,[11] and convulsions.[12] Therefore, the symptoms in our case may represent a paradoxic reaction to TRH.

During the second relapse in the current case, we expected that the influence of phenytoin on thyroid function would be removed along with the change of anticonvulsant to valproate. However, the thyroid function was still on a low level when the third relapsing broke out. Thyroxine replacement therapy effectively controlled symptoms in our patient who only had mild hypothyroidism. Likewise, thyroxine replacement therapy, which suppresses the secretion of endogenous TRH, improved symptoms of Hashimoto's encephalopathy in some cases.[4,13] On the basis of these findings, TRH may have an important role in Hashimoto's encephalopathy.

Although TRH levels appeared to be associated with hypothyroidism in our case, many other causes of hypothyroidism are known. In addition, high serum levels of TRH and TSH must also be seen in primary hypothyroidism of other causes, but no cases of Hashimoto's encephalopathy have been identified in this group of patients. This type of encephalopathy has been observed only in cases of Hashimoto's thyroiditis. Some cases of Hashimoto's encephalopathy have been treated effectively with steroid therapy.[1] Some patients with Hashimoto's encephalopathy demonstrated a positive thyroid microsome antibody. However, there was no link between a change in the microsome antibody titers and the relapses of symptoms.[1,4] On the basis of these findings, as well as those in the current case, an unknown autoimmune antibody may be related to the effect of TRH.

Our case experienced three relapses closely associated with four cycles of menstruation. This association has not been described previously. However, we observed no relation between relapses and levels of gonadotropic or gonadal hormones, suggesting that the brain center that regulates the menstrual cycle may affect TRH receptors directly. Further investigation is needed to clarify the relation between relapses of Hashimoto's encephalopathy and the menstrual cycle.

Thyroxine replacement therapy without steroid therapy effectively controlled symptoms in our patient. This study was the first trial of TRH in a patient with Hashimoto's encephalopathy. Additional trials are needed to investigate the TRH-related mechanism of Hashimoto's encephalopathy.

Table 1. Duration and Amplitude of Myoclonus in Right Biceps Muscle

TRH injection dose	Remission Phase		Excerbation Phase	
	Duration	Amplitude	Duration	Amplitude
0 mg	—	—	—	1 mV
0.5 mg	7 min	0.8 mV	7 min	1.3 mV
2 mg	13 min	1.5 mV	13 min	1.7 mV

TRH, thyrotropin-releasing hormone.

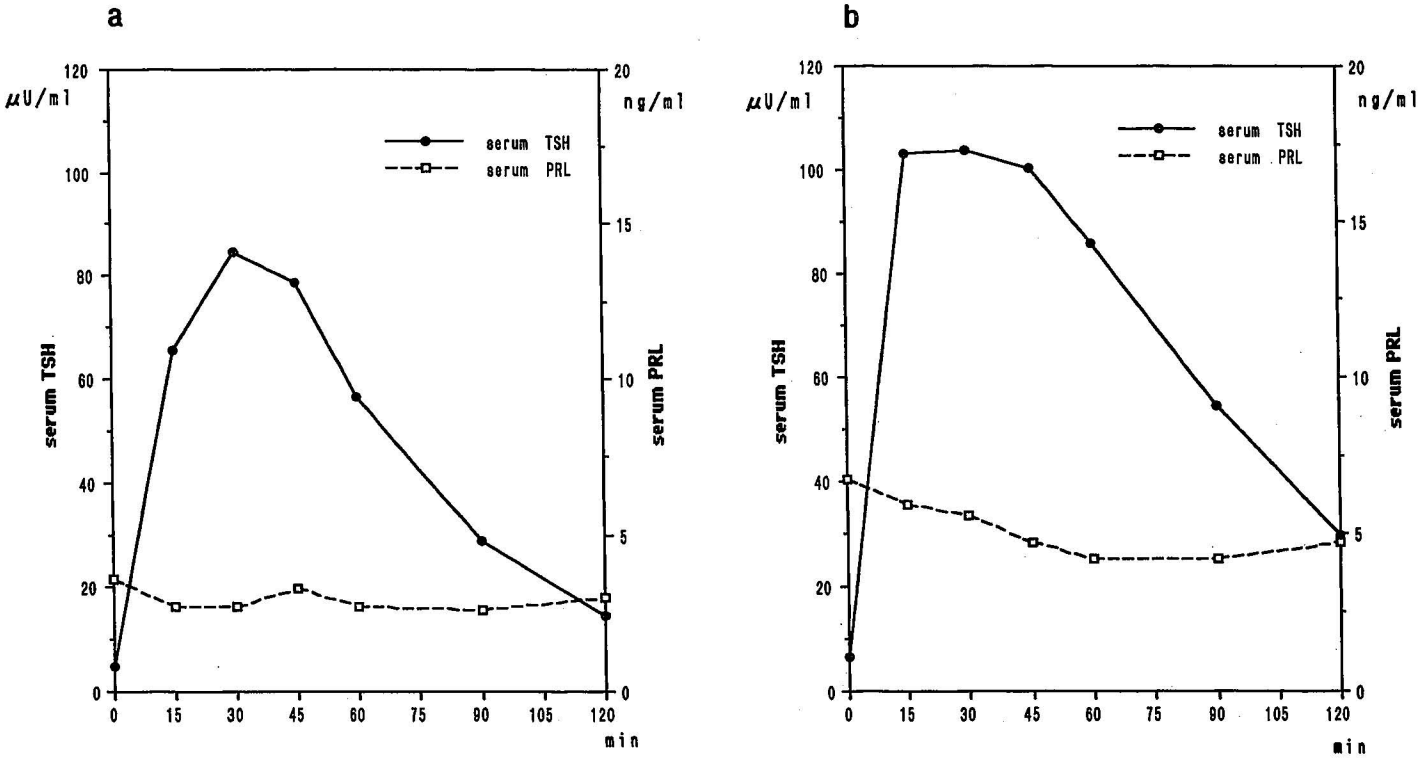

Figure 3. Serum thyroid-stimulating hormone (TSH) and prolactin (PRL) responses by thyrotropin-releasing hormone venous administration. **a:** 0.5-mg thyrotropin-releasing hormone administration. **b:** 2-mg thyrotropin-releasing hormone administration.

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