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THE EFFECTS OF THYROTROPIN RELEASING HORMONE ON AMYOTROPHIC LATERAL SCLEROSIS: A CLINICAL AND PHYSIOLOGICAL STUDY

Itsuro KOBAYASHI, Eiko KITAMURA, Kiyomi YAMANE and **Shoichi MARUYAMA**

Department of Neurology (Director: Prof. Shoichi MARUYAMA), Neurological Institute, Tokyo Women's Medical College

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Abstract

TRH-T treatment was studied in 38 cases of ALS for two weeks, and its effects were evaluated clinically and physiologically before and after administration.

Thirty-eight patients of ALS were 26 men and 12 women, and mean age, age of onset and duration of illness were 53.6, 51.9 years old and 1.5 years, respectively.

Subjective and/or objective improvements were found in 21 cases (55%). Two groups were divided into effective (21 cases) and noneffective (17 cases) groups.

Mean age, age of onset and duration of illness were 56.4, 55.0 years old and 1.4 years in the effective group, whereas 50.3, 48.1 years old and 2.4 years in the noneffective group. There was statistical significance ($p<0.05$) of prolongation on duration of illness in the noneffective group.

Clinical findings, such as bulbar sign, respiratory disturbance, muscle atrophy and pyramidal sign, were not different between effective and noneffective group.

Physiological examinations by means of spinal reflex were done with F-wave and H-reflex techniques. No significant changes were observed before and after treatment in two groups.

H-reflex recovery curves were drawn before and 15 and 30 minutes after intravenous injection of 6 mg of TRH in 14 cases.

H-reflex recovery curve revealed a facilitating effect on 15 and 30 minutes after TRH administration in effective group.

A skeletal muscle biopsy revealed mainly neurogenic changes, partly myogenic changes, but these changes were observed in both effective and noneffective groups. There were 6 cases whose CK levels were elevated.

These data may suggest that TRH works as a neurotransmitter and a neuromodulater in spinal anterior horn cells.

Introduction

Amyotrophic lateral sclerosis (ALS) is a tragic disease with extremely poor prognosis caused by quite unknown factors. Many attempts have been performed thus far but certainly effective therapy is not yet found. Engel et al[1)~3)] and Munsat et al.[4)] found therapeutic effects of thyrotropin releasing hormone (TRH) by intravenous, subcutaneous, or intrathecal injection of a large dose. On the other hand, Saida et al.[5)] and Mitsumoto et al.[6)] did not find the effects of TRH.

Recently, double blind trials revealed the effects of TRH on ALS[7)~9)].

We had reported the effects of TRH shown by intramuscular and/or intravenous injection of a small doses (0.5~2 mg) from 1978 to 1986[10)]. Now we performed physiological function tests before and after injection of 0.5 to 8 mg of TRH in additional cases in order to study its chronic effects and examined changes in H-reflex recovery curve in order to investigate the acute therapeutic effects of intravenous injection of TRH.

Subjects and Methods

Subjects were 38 inpatients (26 men and 12 women) with ALS in our department. Age, age of onset, and duration of illness (mean ± S.D.) were 53.6 ± 11.3, 51.9 ± 11.3, and 1.5 ± 1.0 years, respectively. The diagnosis of ALS was based on clinical evidence of both upper and lower motor neuron abnormality with electrodiagnostic evidence of widespread active denervation and chronic motor unit changes in spite of normal nerve conduction velocity. None of patients had dementia, nor cerebellar nor sensory abnormalities (Table 1).

Table 1 Subjects and treatment of TRH (thyrotropin releasing hormone)

	Dose (mg)		Duration (weeks)	Effects and/or side effects
Effective				
1. FO	2	IM	2	Able to lift up arms
2. EN	2	IM	2	Grasping power 1→5kg
3. MM	1	1M	1	Specch & gait disturbance ↓ Able to lift arms
4. HF	2	IM	2	Able to lift up arms
5. KK	1	1M	2	Specch & swallowing disturbance ↓
6. JS	2	IM	2	Grasping power 10→15kg
7. YK	1	IV	2	Grasping power 12→20kg
8. IS	2	IM	2	Power up muscle strength
9. HT	0.5	IM	2	Dysarthria ↓
10. KS	2	IM	2	Grasping power 0→4kg
11. SS	6	IM	2	Grasping power 0→2kg
12. YS	8	IM	2	Grasping power 8→12kg
13. IM	8	IM	2	Dysarthria ↓, Grasping power 11→15kg
14. IO	8	IM	2	Dyspnea ↓
15. NI	8	IM	2	Power up muscle strength
16. SS	8	IM	2	Fasciculation ↓
17. AS	8	IM	2	Dysphagia ↓, Fasciculation ↓
18. HK	8	IM	2	Dysphagia ↓
19. IU	8	IM	2	Speech & swallowing disturbance ↓
20. MN	8	IM	2	Power up muscle strength
21. TO	8	IM	2	Dysphagia ↓
Noneffective				
22. KM	0.5	IM	2	
23. CN	1~2	IM	2	
24. HS	1	1M	2	
25. MN	1	1M	2	
26. SH	1~10	IM, IV	4	
27. MY	2	IM	2	Dyspnea, Palpitation
28. SK	2	IM	2	
29. YI	2	IM	2	
30. YT	0.5~2	IM	2	Arrhythmia
31. SO	2	IM	4	
32. HS	6	IV	2	Fasciculation ↑
33. TT	8	IM	2	Muscle power ↓
34. CU	2	IM	2	Muscle power ↓
35. KK	8	IM	2	
36. KM	8	IM	2	
37. HG	8	IM	2	
38. II	8	IM	2	

IM : intramuscular injection, IV : intravenous injection

F and H waves were studied before and after administration of TRH in order to check spinal function. For determination of F wave, right median nerve was supra-maximally stimulated to lead the first (M) and the second (F) waves from short abductor muscle of thumb. F-wave conduction velocity (m/sec) was calculated from the latency period of F wave and the length of an upper extremity according to Kimura's method[11] and F/M ratio from the leatency periods of M and F waves[12].

For determination of H wave, internal popliteal nerve was submaximally stimulated with a recording electrode located on the triceps muscle of calf to induce two waves: the first early wave is M wave and the second late wave is H wave.

H-reflex recovery curves were drawn before and 15 and 30 minutes after intravenous injection of 6 mg (14 cases) of TRH over a period of 30 minutes to investigate the time for conditioning (first) reflex (H_1) to influence test (second) reflex (H_2).

Muscle biopsy was obtained from 33 patients to make (1) paraffin preparation used for hemaoxillin-eosin (HE) and Masson trichrome staining and (2) cryostat preparation (fresh frozen sections) used for histochemical test.

TRH was offered by Takeda Pharmaceutical Company (Osaka) and used at the doses and over the durations listed in Table 1.

Results

1. Effects of TRH (Table 1)

TRH was effective in 21 of 38 patients with ALS (55%): objective improvements were capability of lifting arms and strengthened grasping power; subjective effects were easy to speak, swallow, breathe, and walk. Aggravated dyspnea, palpitaiton, arhythmia, increased fasciculation and lowered muscular strength were found in noneffective cases.

2. Patient age, age of onset, duration of illness, and clinical symptoms (Table 2)

Patient age, age of onset and duration of illness were 56.4 ± 10.0, 55.0 ± 10.2, and 1.4 ± 0.8 years (mean ± S.D.), respectively in the effective group; and 50.3 ± 12.0, 48.1 ± 11.7, and 2.4 ± 1.3 years, respectively in the noneffective group. The duration of illness was significantly shorter in the effective group than the noneffective group ($p<0.05$). Clinical conditions were divided into four categories; no symptom (−), mild (±), moderate (+), and severe (#); and related to the effects of TRH (Table 2). In terms of bulbar and respiratory disorders, similar distributions were found in both effective and noneffective groups without significant difference. However, TRH was more effective in the patients with lower motor neuron involvement; severe damage of lower motor neuron was found in 57% of the effective group and 41% of the noneffective group. As regards upper motor neuron, there was no difference between the effective and noneffective groups.

3. Variation in F and H waves (Tabel 3 and 4)

In both groups, TRH treatment did not change M or F wave, F/M ratio, or potency period of H wave. F wave was not evoked before the treatment but was evoked after the treatment in only one case of the effective group. On the contrary, F wave which was evoked before the treatment was not evoked after the treatment in two cases.

In two cases of the noneffective group, F wave was not evoked before as well as after the treatment.

4. H-reflex recovery curve (Figs. 1 and 2)

The shaded areas in Figs. 1 and 2 represent the range of means ± 2 S.D. in 10 normal controls. Solid lines and closed circles are mean values before loading in 14 patients of the effective and noneffective groups. The "x" marks and open circles indicate averages 15 and 30 minutes after TRH loading.

Fig. 1 shows H-reflex recovery curve in the effective group, which indicates initial facilitation and shortening of refractory periodis at 30~100 msec without exciting period.

In the noneffective group (Fig. 2), initial inhibition was caused and the refractory period was prolonged by TRH loading. The exciting period was not found.

Table 2 Clinical symptoms of ALS (amyotrophic lateral sclerosis)

	Age (years)	Onset of illness (years)	Duration of illness (years)	Bulbar sign	Respiratory disturbance	Disturbance of	
						Upper motor neuron	Lower motor neuron
Effective							
1. FO	52	51	1	+	−	++	++
2. EN	61	60	1	++	−	±	++
3. MM	55	53	2	+	−	+	+
4. HF	31	30	1	−	−	++	++
5. KK	48	47	1	++	−	+	++
6. JS	62	61	1	++	±	++	++
7. YK	50	50	0.5	−	−	+	+
8. IS	63	62	1	+	−	+	+
9. HT	60	60	0.5	+	−	+	+
10. KS	51	50	1	+	−	+	+
11. SS	60	59	1	+	−	++	++
12. YS	72	71	1	−	−	+	+
13. IM	44	41	3	+	−	+	−
14. IO	54	52	2	+	++	±	++
15. NI	49	48	0.8	−	−	−	++
16. SS	61	58	3.3	−	−	−	++
17. AS	48	45	2.8	−	±	±	+
18. HK	65	64	1.3	−	+	+	++
19. IU	74	73	1.3	++	+	+	+
20. MN	55	53	1.3	+	+	+	++
21. TO	68	67	1.3	+	+	+	++
Noneffective							
22. KM	45	42	3	+	+	−	++
23. CN	64	62	2	+	−	+	+
24. HS	50	46	4	−	−	+	+
25. MN	37	34	3	+	−	+	+
26. SH	36	35	1	−	−	++	+
27. MY	61	59	2	++	−	+	++
28. SK	62	60	2	++	+	+	++
29. YI	72	69	3	++	−	−	+
30. YT	53	52	1	−	−	±	+
31. SO	29	27	2	−	−	±	+
32. HS	65	60	5	++	++	+	++
33. TT	43	40	3	++	+	++	++
34. CU	46	45	1	−	−	±	++
35. KK	56	55	1.4	+	+	+	+
36. KM	54	52	1.5	+	−	+	+
37. HG	41	40	0.8	−	−	−	+
38. II	41	39	2	++	−	±	++

− : none, ± : mild, + : moderate, ++ : severe

5. Findings of muscle biopsy and effects of TRH (Table 5)

Table 5 lists sites of muscle biopsy and pathologic changes. Clear relation was not found between pathologic changes of the muscle and TRH treatment. Enhanced creatine phosphokinase (CK) level was observed in 5 of noneffective cases.

Discussion

In treatment of ALS, TRH was reported to improve subjective and objective clinical conditions by Engel et al.[1)~3)], Munsat et al.[4)], Caroscio

Table 3 F-wave changes before and after TRH (thyrotropin releasing hormone)

	M msec	Before F		F/M ratio	M msec	After F		F/M ratio
		msec	m/sec			msec	m/sec	
Effective	2.9 ±0.7	26.9 ±3.8	58.9 ±2.4	4.1 ±1.1	2.9 ±0.6	26.8 ±4.0	56.8 ±2.6	4.0 ±0.4
Absence of F wave (case)		1				2		
Noneffective	2.9 ±1.0	28.6 ±1.9	53.4 ±5.0	4.4 ±1.3	3.5 ±1.4	27.7 ±2.2	57.8 ±8.6	3.3 ±0.9
Absence of F wave (case)		2				2		

Table 4 H-wave changes before and after TRH (thyrotropin releasing hormone)

	Before(msec)	After(msec)
Effective	28.9±2.9	28.6±2.6
Noneffective	31.6±3.0	32.3±4.5

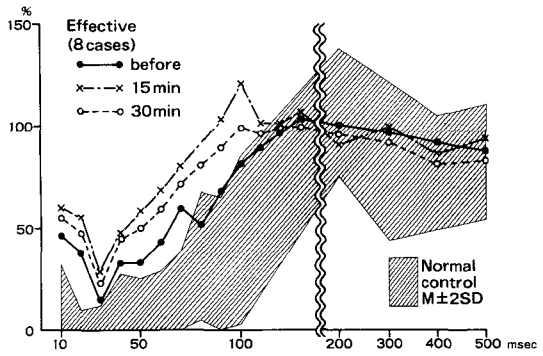

Fig. 1 H-reflex recovery curve before and after TRH (6 mg) administration (effective cases).

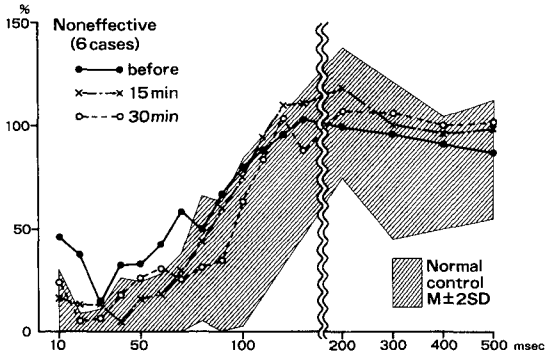

Fig. 2 H-reflex recovery curve before and after TRH (6 mg) administration (noneffective cases).

et al.[7], and Yamane et al.[10], and to temporally strengthen muscular force by Brooke[8]. Some investigators did not find the effects of TRH[5)6)9)]. We observed the subjective and objective effects in 55% of the present patients as well as in other reports, in particular, enhanced grasping power was a remarkable objective improvement.

Differences between the effective and the noneffective groups were studied from a variety of viewpoints.

There were no differences in patient age and age of onset between both groups but the noneffective group tended to be younger. Duration of illness was significantly longer in the noneffective group than in the effective group ($p<0.05$). These findings may be important in considering the therapeutic effects of TRH; TRH is more dificult to exhibit its effects in patients who had early onset and have the disease for longer period.

There are no reports of the relation between clinical conditions and the effects of TRH. We did not find clear correlation of TRH effects to degrees of bulbar sign, respiratory disorder, and damage in upper and lower motor neurons. However, TRH was more effective in the patients with ALS who had more damaged lower motor neuron. This finding suggested stronger effects of TRH on lower motor neuron or on and distal to anterior horn cells.

Here it comes into question that Engel et al.[1)~3)], Munsat et al.[4], and Caroscio et al.[7] used as large amounts as 25 to 500 mg of TRH while Yamane et al.[10] and we found the effects with as small

Table 5

	Section of muscle	Findings	CK
Effective			
1. F O	Triceps	B	N
2. E N	Triceps	B+D	N
3. MM	Triceps	B+C	N
4. H F	FCU	B+C+D	N
5. K K	Triceps	B+D	N
6. J S	Deltoid	B+D	N
7. Y K	Triceps	B+C+D	N
8. I S	Not examined		N
9. H T	Triceps	A+B	N
10. K S	Triceps	B	N
11. S S	Triceps	B+C+D	N
12. Y S	Triceps	B+C+D	N
13. I M	Triceps	B+C	N
14. I O	ECR	B+C	N
15. N I	Quadriceps	B+C+D	N
16. S S	Not examined		N
17. A S	Triceps	B	N
18. H K	Triceps	A	N
19. I U	Tibialis anterior	B	N
20. MN	Tibialis anterior	B+C	298
21. T O	Triceps	B+D	N
Noneffective			
22. KM	Triceps	B+C+D	N
23. C N	Deltoid	B+C+D	336
24. H S	Peroneal	B+D	182
25. MN	Quadriceps	B+D	454
26. S H	Triceps	B+D	543
27. MY	Triceps	B	N
28. S K	Triceps	B+C+D	N
29. Y I	Triceps	A	N
30. Y T	Quadriceps	B+C	N
31. S O	Triceps	B	N
32. H S	Quadriceps	B+D	134
33. T T	Triceps	C	N
34. C U	Triceps	B	N
35. K K	Not examined		N
36. KM	Quadriceps	B	N
37. H G	Not examined		236
38. I I	Not examined		N

A : Small angulated fiber
B : Small grouped atrophy
C : Large grouped atrophy
D : Mixed with myogenic change
N : Normal

amounts as 0.5 to 8 mg. The reason for the discrepancy is unknown but it is described that TRH is effective in spinocerebellar degeneration by intramuscular injection of 0.5 mg in Japan[13]. If TRH acts as a neurotransmitter and neuromodulator for nervous cells, it is expected to be effective even at low concentrations.

TRH is used to treat ALS (1) because of it has a distribution in brain-stem nuclei and anterior horn cells and acts as a neurotransmitter and neuromodulator[14], (2) because of TRH has a wide distribution in human spinal cord with the highest concentration in anterior horn cells while TRH level is lowered in the patients of ALS[15], and (3) decreased TRH level in the cerebrospinal fluid of ALS patients is increased by intravenous administration of the TRH[16].

On the other hand, there are few subjective and objective methods of evaluating functions of the spinal cord, in particular, anterior horn cells. Development of F wave is considered to result from excitation of alpha motoneuron by antidromic stimulation[17]. H wave is induced by excitation of the group Ia fiber by electric stimulation from the muscle spindle of the agonist, used as an indicator of irritablility of alpha motoneuron, and influneced by different inputs[18]. Recovery of H wave is accelerated by enhanced irritability of spinal alpha motoneuron and retarded by the lowered irritability[18].

TRH treatment did not change F and H waves possibly because the determination was performed at various time after TRH injection so that TRH level was not sufficiently high in blood or cerebrospinal fluid. F and H waves should be determined at fixed time in further investigation.

On the other hand, the effective group showed initial facilitation and reduction of refractory periods at 30~100 msec on H reflex recovery curves in acute stage before and 15 and 30 minutes after the intravenous injection of TRH. Inhibition of the facilitation and prolongation of the refractory period were found in the noneffective group. The initial facilitation and the reduced refractory period suggested enhanced irritability of alpha motoneuron, that is, these findings in the effective group appeared to indicate that TRH increased the irritability of alpha motoneuron in the patients with ALS.

Pathologic changes in muscular tissue is mean-

ingful information of severity of ALS. At the same time, we investigated identification of diseases related to ALS and distal myopathy.

Constant relation to changes in muscular tissue was not found in either effective nor noneffective group. However, the CK level was increased in 5 patients of the noneffective group. In ALS, it is reported that the enhanced CK level results from myogenic changes and related to degeneration of anterior horn cells[20]. The present cases with enhanced CK level showed myogenic changes as well. However, slight myogenic changes were found in some cases without increased CK level whether TRH was effective or not. The increased CK level in the cases in whick TRH was noneffective suggested intensive degeneraiton of anterior horn cells besides relatively severe changes in muscular tissue. TRH may not appear to exhibit its effects on these changes.

Conclusion

1) Subjective and obejctive improvements were shown in 21 patients (55%) by injection of 0.5 to 8 mg of TRH for 1 to 2 weeks.

2) TRH was more effective in the patients who had the disease for shorter period.

3) TRH treatment did not change the latency periods of F and H waves in either effective or noneffective group.

4) Facilitation was observed in H-reflex recovery curves 15 and 30 minutes after the intravenous injection of TRH in the effective group.

5) Various changes were found in the muscular tissue with no constant tendency in both effective and noneffective groups. TRH was noneffective in the cases with high CK level.

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筋萎縮性側索硬化症に対する thyrotropin releasing hormone tartrate (TRH-T) の治療効果と臨床生理学的検討

東京女子医科大学　脳神経センター神経内科
小林　逸郎・北村　英子・山根　清美・丸山　勝一
(コバヤシ イツロウ　キタムラ エイコ　ヤマネ キヨミ　マルヤマ ショウイチ)

筋萎縮性側索硬化症患者38例に thyrotropin releasing hormone tratrate (TRH-T) を0.5～8mg 2週間投与し，治療効果と神経生理学的所見の検討を行なった．自・他覚的に改善の認められた有効例は21例 (55%) であった．有効例では無効例に比べて罹病期間が有意 ($p<0.05$) に短かった．臨床症状では，有効，無効ともに同じような分布を示して差異はなかった．TRH-T 2週間治療前後では，F波，H波の潜時に変化は認められなかった．しかし，有効例において，TRH-T 6mg 静注15分，30分後にH波回復曲線の促通化が認められた．筋組織では有効・無効例にかかわらず，種々の変化を示し，一定の傾向は認められなかった．また，creatine phosphokinase (CK) 高値を示す症例では，TRH-T の効果は認められなかった．