의학석사 학위논문

Analysis of Muscle Fiber Conduction Velocity in Thyrotoxic Periodic Paralysis

갑상선 중독 주기성 마비에서 근섬유 전도속도의 분석

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ABSTRACT

Introduction: Thyrotoxic periodic paralysis (TPP) is a disease characterized by reversible episodes of paralysis with hypokalemia under hyperthyroidism. The clinical pictures of TPP are similar with hypokalemic periodic paralysis (HOPP), which is caused by malfunctions of ion channels in muscle membranes thus showing delayed muscle fiber conduction velocity (MFCV). However, the specific mechanism for TPP is largely unknown. We investigated whether or not TPP has a dysfunction at the level of muscle membrane as HOPP by measuring MFCV.

Patients and methods: Thirteen men with TPP and fifteen age-matched healthy controls were included in this study. We assessed clinical characteristics and performed serial neurophysiologic tests including nerve conduction studies, prolonged exercise tests (PET) and MFCV.

Results: In TPP, MFCVs were not delayed, while MFCVs seemed to be faster till one year after attack. In conditions with positive PET, MFCVs were faster compared with conditions with negative PET. However, hypokalemia or hyperthyroidism seemed to cause no significant effects on MFCVs. MFCV values were negatively correlated with potassium level, days from attack, and some values of sensory nerve conduction studies.

Conclusion: Although clinical manifestations are similar with HOPPs, TPP seems to have different mechanisms not delaying MFCV but facilitating MFCV. Our study implicates that TPP does not seem to have malfunctions of ion channels associated with delaying muscle fiber conduction. It may be related to some factors facilitating muscle fiber conduction such as nerve excitability. Further studies are needed to support our preliminary results.

Keywords: Thyrotoxic periodic paralysis, muscle fiber conduction velocity.

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CONTENTS

Introduction

Thyrotoxic periodic paralysis (TPP) is a secondary periodic paralysis, as a complication of hyperthyroidism characterized by muscle paralysis and hypokalemia due to intracellular shift of potassium.[1] The TPP is most commonly seen in men of Asian descent, despite the fact that hyperthyroidism is 10 times more common in women especially in iodine-replete communities.[2] Other many clinical presentations and physiologic features are similar to those of primary hypokalemic periodic paralysis (HOPP).

The pathophysiology of muscle paralysis in hypokalemic periodic paralysis is paradoxical depolarization.[3] In vitro microelectrode study using biopsied muscle obtained from a TPP patient showed paradoxical depolarization of the resting membrane potentials, as occurs in familial HOPP.[4] In addition, the prolonged exercise test (PET) shows a significant decrease in compound motor action potential (CMAP) amplitude in both forms of periodic paralysis.[5] [6] [7] Even in the euthyroid state, the time-dependent CMAP decline of TPP still exists but less than in hyperthyroid state.[7] These findings support that familial HOPP and TPP have the similar underlying pathophysiological mechanism. However, specific mechanism for TPP remains unclear. The muscle fiber conduction velocity (MFCV) testing is a sensitive and reliable technique having high diagnostic yield in detecting various myopathy and channelopathy.[8] In familial HOPP, MFCV slowing provided supportive information in diagnosis other than familial history and clinical symptoms.[9] [10] In contrast to familial HOPP, there was one previous study demonstrating the

MFCV was normal in two TPP patients.[11] The purpose of this study was to investigate whether or not there is dysfunction at the level of muscle membrane in TPP as familial HOPP by measuring MFCV and to elucidate mechanism of TPP.

Methods

Patients and Controls.

This prospective study was approved by the local human Research Protection Office/Institutional Review Board. All subjects were provided informed consent. Thirteen Korean men with TPP (mean age, 35.9 years; ranges, 25–59 years), and fifteen age-matched healthy controls (8 women, 7 men; mean age, 42.3 years; ranges, 22–61 years) were enrolled. The diagnosis of TPP was based on the presence of paralytic attacks with hypokalemia and the clinical manifestations of thyrotoxicosis with elevated serum thyroid hormone.

Electrophysiologic Evaluation

Subjects were tested by nerve conduction studies and MFCV performed using Nicolet® Viking electromyography equipment with standard filter settings. We also performed prolonged exercise test (PET) in all subjects at the same time. In five patients, MFCV, nerve conduction studies, and PET were done serially.

Muscle-Fiber Conduction Velocity Measurement

Invasive MFCV measurements were performed in the tibialis anterior muscle by means of needle electrodes adapted from the modified method of Troni et al. 1983.[12] In brief, muscle fibers were stimulated at the proximal two thirds point of the tibial anterior muscle by a small monopolar needle electrode (26G, surface area 0.34mm^2; Teca, Oxford Instruments, Old Woking, UK)

(cathode) using a surface electrode as anode 30mm distally. This muscle was appropriate for the study because of its size, accessibility, longitudinally orientated muscle fibers, and the eccentric location of the end plate in relation to the muscle belly. The recording electrode was placed proximally at a distance 50 mm by a monopolar needle electrode. Both needles were inserted to a depth of about 20 mm perpendicular to the skin surface and maintained in a perpendicular position. A surface ground electrode was placed between the needles. MFCV were recorded using filter settings 500 to 10 kHz. Responses were frequently acquired with stimulation beginning at low intensity, typically between 1 and 3 mA (with stimulus duration of 0.1 ms). If there were no response, the needle was repositioned along the 50-mm arc. Onset latencies earlier than 8 ms were likely to be conducted via intramuscular nerve twigs and were not included.[13] After optimal waves recorded, negative peak latencies of all spikes exceeding 20 μV in amplitude were transformed into the velocities, using the distance, between the points of insertion of the stimulating and the recording electrode as estimate of the propagated distance. The latency of each muscle fiber action potential was measured and calculated. The fastest MFCV, slowest MFCV, mean MFCV and the fastest/slowest ratio (F/S ratio) representing the scatter of conduction velocities were used as parameters. Fig. 1 represents an example of invasive MFCV measurement.

Prolonged Exercise Test

The exercise test is useful in confirming the diagnosis of periodic paralysis correlated with abnormal excitability of muscle membrane, but does not

distinguish the type or mechanism, as already pointed out by earlier authors.[5] [6] The test was always done at the same day of MFCV test. The hand was immobilized on an arm board to minimize artifacts in CMAP amplitude resulting from electrode movement. Supramaximal stimulation of ulnar nerve was obtained with a bipolar stimulator attached to the wrist. Using standard techniques and surface electrodes, CMAPs in the abductor digiti minimi were recorded every minute for five minutes to obtain baseline amplitude. The patient was then asked to contract the muscle isometrically for five minutes as hard as possible. At the completion of the exercise, the patient was instructed to relax completely while CMAP responses to single shocks were recorded every minute until stabilization of the decrement (usually 40 to 50 minutes). The percentage changes in amplitude were calculated according to McMannis et al.[5]

Statistics

All statistical analysis was performed with IBM SPSS statistics 20 (SPSS, Inc., Chicago, IL, USA). Comparisons between groups were performed with student t-test, Wilcoxon rank sum test, or Mann-Whitney test when appropriate. Correlation analysis was made using parametric Pearson's coefficient (r). $P < 0.05$ was deemed to indicate statistical significance.

Results

Patients

The thirteen TPP men and fifteen healthy controls were included in the study and baseline demographics are summarized in the Table 1. All TPP men had experienced one or more episodes without family history of periodic paralysis. The episodes were induced by a heavy carbohydrate meal, steroid injection, or resting after strenuous exercise. Weakness involved lower extremities more common and progressed invariably below Medical Research Council (MRC) Scale grade 3. Muscles innervated by cranial nerves were not involved. Thyroid function test showed high T3, high FT4, and suppressed TSH level.

Prolonged exercise test (PET)

In healthy subjects, significant CMAP amplitudes changes were not seen after prolonged exercise. In TPP, decline above 40 % were seen in nine of thirteen patients (69.2%) after exercise. Among all 27 PETs in TPP patients, positive PETs were seen in 20 PETs (74.1%). PETs changed from positive to negative in 3 of 5 patients serially tested. Positive PETs were observed even after 1 year from the attack, while the time to significant decline seemed to be delayed according to days from attack (within one week: 43.4±22.1 minutes vs after 1 year: 86.0 ±44.2 minutes, p=0.055).

MFCV

The normal value of MFCV derived from our healthy controls was close to the values published in the previous literatures.[12 14 15] The mean MFCV was

3.61 (±0.58) m/s and the F/S ratio was 1.00 (±0.01) in healthy controls. Although age or gender turned out to be a differentiating factor in previous studies[16], there was no significant difference after correcting the two variables.

In thirteen patients, five patients were evaluated serially, so total 22 MFCV results were collected. There were statistically significant differences for fastest MFCV (4.17±0.60 m/s), mean MFCV (3.91±0.55 m/s) and F/S ratio (1.14±0.13) except slowest values of MFCV between patients and controls (Table 2, Fig 2). When compared to male controls, these trends were not changed. MFCVs in TPP were not delayed but faster compared to normal controls.

MFCV changes were reanalyzed by dividing intervals from attack. The trends of faster MFCV in TPP seemed to disappear after one year from attack (Table 2, Fig. 3). There was also a significant negative correlation between the days from attack and mean MFCV ($r=-0.445$, $p=0.043$). Furthermore there were significant differences in MFCV between group of each period and group after one year from attack (Table 2, Fig. 3). The MFCV values and F/S ratio were more increased in any time within one year compared to controls. However, beyond the one year, the relevance gradually disappeared. It is hard to find a statistical significance with existing data comparing attack and inter-attack MFCV, because only the two patients were evaluated electrophysiologically on attack day.

Noticeable differences of MFCV values were seen, depending on whether the PET results were positive or not. In conditions with positive PET, MFCVs were significantly faster than those in conditions with negative PET

(Table 3, Fig. 4).

The negative correlation was observed between MFCV values and the sensory nerve conduction values. Fast MFCV was correlated with ulnar sensory nerve conduction velocity (r=-0.689, p=0.040) and sural nerve amplitude (r=-0.756, p=0.018). Mean MFCV was correlated with median sensory nerve conduction velocity (r=-0.678, p=0.045) and sural nerve amplitude (r=-0.807, p=0.009). F/S ratio was correlated with sural nerve amplitude (r=-0.678, p=0.045). These suggest some relations between faster MFCVs and dysfunctions of sensory nerve in TPP. F/S ratio was correlated with serum potassium level (r=-0.445, p=0.043). However, there were no differences in MFCV values between groups with abnormal and normal serologic tests. (Table 3)

Discussion

The pathophysiology of skeletal muscle paralysis in TPP is still controversial. It includes a genetic predisposition, thyrotoxicosis and environmental factors and the relative influence from each of these factors. The traditional explanation is that muscle fiber membrane should depolarize under low extracellular K+ conditions leads to inactivation of sodium channels.[1] [17] In familial Hypokalemic periodic paralysis, paradoxical depolarization is caused by mutations in the Cav1.1 voltage-gated Ca+ channel or the Nav1.4 Na+ channel.[18] Recently, several studies suggested that TPP is partially associated with the mutations in the gene encoding Kir2.6, a skeletal muscle-specific Kir channel and predispose patients to acute paralytic attacks.[17] Loss of function of Kir2.6 together with increased activity of Na+/K+ ATPase may induce positive feed-forward cycle of hypokalemia, leading to paradoxical depolarization with consequent inactivation of Na+ channel and muscle inexcitability.[17] [19] Additionally, several different genes have been reported to be associated with TPP.

The results of histological examination of muscles in TPP and familial HOPP have been more distinctive supporting they are not unified disease. TPP have been described such features as sarcolemmal masses, atrophy and degeneration of muscle fibers, invasion by macrophages and lymphocytes-the latter sometimes forming lymphorrhages and fatty infiltration[20] [21] whereas, it is much more distinguishing features showing increase of connective tissue, moderate fiber size variability, rare necrotic fibers and a large number of vacuoles in familial HOPP.[22] [23]

The values of invasive MFCV testing have been documented previously because of its several advantages. It measures dynamic muscle functions in both type I and type II fibers unlikely needle EMG estimates biased by type I motor units.[15] Moreover, irrespective of the state of innervation, it provide objective and quantitative results with the non-volitional, direct activation of the resting muscle.[10] Considering muscle fiber diameter and overall membrane function affect the outcome of the values, myopathies that have channel dysfunction in the muscle-fiber membrane can lead to inexcitability associated with reduced MFCV. By contrast, neuropathic disease with signs of reinnervation at needle EMG or ALS showed increased range of velocities combination shorter and longer latencies compared to the normal control. It had been explained by concurrent slow conducting atrophic fibers and reinnervated hypertrophic fibers compensating the force loss resulting in an increased F/S ratio.[24] [25] Although, it is unknown how far MFCV changes related with total or partial denervation and reinnervation, after reinnervation had started, the mean MFCV seems to be increased. In familial HOPP, reduced MFCV has been raised a sensitive marker for the detection of membrane muscle fiber defects suggesting to be an additional diagnostic criterion of disease.[9] Hence, we anticipated deriving the characteristic results of MFCV providing pathophysiologic clues for TPP.

In this study we have demonstrated several novel electrophysiologic findings for TPP. First of all, MFCVs were not delayed as expected, but MFCVs were faster than normal. Furthermore, the values of MFCV tend to be normalized after certain time from attack in contrast with familial HOPP which showed delayed MFCV consistently in previous studies.[9] [10] Dynamic

changes of MFCV were found through serial exams for the first time. In addition, increased MFCV in the asymptomatic period were shown compared to control group although the results are getting similar over one year. The distinguishable MFCV results of TPP patients after and induced attack of muscle paresis can be interpreted that there is different kind of underlying pathophysiologic mechanism.

Secondly, MFCV was faster in PET positive conditions compared with PET negative conditions. These reflect that the nerve or muscle excitability changes assuming that abnormal features of positive test may be associated with faster MFCVs in TPP. In other words, the MFCV values are more distinctive when the underlying neuromuscular dysfunction showed.

We found significant negative correlations between the sensory nerve functions and the MFCV values. These results suggest that the sensory nerve excitability may be altered with faster MFCV changes in TPP. According to the previous studies, hypokalemia do not trigger paradoxical depolarization in muscle membrane only, but also in nerve axon or motor neurons.[26] [27] [28] Acute decrease in the serum K+ level would result in muscle membrane hyperpolarization, and thus lead to failure of generation of muscle action potentials. At the same time, peripheral nerve axons would probably also be hyperpolarized by hypokalemia.[26] In previous studies, axonal hyperpolarization consequent reduced excitability of axons were reported, not only CMAP amplitude reduction, but also CMAP temporal dispersion in several nerves were shown.[29] Inshasi et al. described functional impairment of sensory nerves, as well as motor units, which recovered concomitantly with

normalization of serum K+ in patients with periodic paralysis during attacks.[27] They suggested the possible mechanism of the experimental result that involvement of sensory nerves arised through dorsal root ganglia having an incomplete blood-nerve barrier and sensory neurons being particularly vulnerable to derangements affecting nerve cell metabolism. Neuronal inexcitability consequent upon possible inactivation of the sodium–potassium pump by the low concentration of extracellular potassium may occur. In our data, the patients showed the elevation of the fastest, mean MFCV and increased variation in MFCV. We hypothesis that the reason of the results may be associated with factors controlling membrane conduction such as nerve excitability or hypertrophic muscle fibers, and their mixture leading to desynchronization of motor unit potential activation and scattered fiber velocities. Hypokalemia as well as hyperthyroidism in itself, bring out peripheral nerve excitability changes[26 27 29], MFCV in TPP may reflect this subclinical peripheral neuropathy, even though it is hard to evaluate of contribution priority between nerve and muscle factor. Although it is estimated that there may be any associations between sensory or motor nerve conduction and MFCV, it is difficult to conclude with current data before adjusting for variables, such as age or days, and because of small number of groups. More studies are needed with additional data to confirmation.

The present study had several limitations. First, the method of measuring MFCV that we used in this study is well established and our values for normal subjects correlate well with those of others. Nevertheless, some sources of error have to be taken into account. Firstly, the calculated conduction velocity is an estimate of the sarcolemmal propagation of an

action potential.[15] A misdirection of the needle electrodes leads to a results variation of 5%-8%. Secondly, the risk of stimulating a nerve fiber cannot be excluded completely. However, we initially excluded the MFCV data over 5m/s that have possibility to be stimulated the nerve twigs. In the last place, type 2 fibers account for about 30% for the tibialis anterior.[30] In rare case, if some patients with extreme type 2 fibers predominant, there is a possibility of underestimation of the results.

Conclusion

Although clinical manifestations are similar with familial HOPP which present delayed MFCV caused by muscle membrane dysfunction, TPP seems to have different mechanisms not delaying MFCV but facilitating fastest MFCV associated with nerve excitability. Our study implicates that TPP may be associated with factors controlling membrane conduction such as nerve excitability. Further studies with lager number of patients are needed to confirm our preliminary results.

References

1. Vijayakumar A, Ashwath G, Thimmappa D. Thyrotoxic periodic paralysis: clinical challenges. Journal of thyroid research 2014;2014:649502.
2. Vanderpump MP. The epidemiology of thyroid disease. British medical bulletin 2011;99:39-51.
3. Cheng CJ, Lin SH, Lo YF, et al. Identification and functional characterization of Kir2.6 mutations associated with non-familial hypokalemic periodic paralysis. The Journal of biological chemistry 2011;286:27425-27435.
4. Hofmann WW, Smith RA. Hypokalemic periodic paralysis studies in vitro. Brain : a journal of neurology 1970;93:445-474.
5. McManis PG, Lambert EH, Daube JR. The exercise test in periodic paralysis. Muscle & nerve 1986;9:704-710.
6. Kuntzer T, Flocard F, Vial C, et al. Exercise test in muscle channelopathies and other muscle disorders. Muscle & nerve 2000;23:1089-1094.
7. Arimura K, Arimura Y, Ng AR, Sakoda S, Higuchi I. Muscle membrane excitability after exercise in thyrotoxic periodic paralysis and thyrotoxicosis without periodic paralysis. Muscle & nerve 2007;36:784-788.
8. Blijham PJ, van Engelen BG, Drost G, Stegeman DF, Schelhaas HJ, Zwarts MJ. Diagnostic yield of muscle fibre conduction velocity in myopathies. Journal of the neurological sciences 2011;309:40-44.
9. Cruz-Martinez A, Arpa J. Muscle fiber conduction velocity in situ in hypokalemic periodic paralyses. Acta neurologica Scandinavica 1997;96:229-235.
10. Troni W, Doriguzzi C, Mongini T. Interictal conduction slowing in muscle fibers in hypokalemic periodic paralysis. Neurology 1983;33:1522-1525.
11. Links TP, van der Hoeven JH. Improvement of the exercise test after

therapy in thyrotoxic periodic paralysis. Muscle & nerve 1993;16:1132-1133.
12. Troni W, Cantello R, Rainero I. Conduction velocity along human muscle fibers in situ. Neurology 1983;33:1453-1459.
13. Allen DC, Arunachalam R, Mills KR. Critical illness myopathy: further evidence from muscle-fiber excitability studies of an acquired channelopathy. Muscle & nerve 2008;37:14-22.
14. Zwarts MJ. Evaluation of the estimation of muscle fiber conduction velocity. Surface versus needle method. Electroencephalography and clinical neurophysiology 1989;73:544-548.
15. Blijham PJ, Hengstman GJ, Ter Laak HJ, Van Engelen BG, Zwarts MJ. Muscle-fiber conduction velocity and electromyography as diagnostic tools in patients with suspected inflammatory myopathy: a prospective study. Muscle & nerve 2004;29:46-50.
16. Lange F, van Weerden TW, van der Hoeven JH. Age-related botulinum toxin effects on muscle fiber conduction velocity in non-injected muscles. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology 2007;118:2398-2403.
17. Falhammar H, Thoren M, Calissendorff J. Thyrotoxic periodic paralysis: clinical and molecular aspects. Endocrine 2013;43:274-284.
18. Matthews E, Labrum R, Sweeney MG, et al. Voltage sensor charge loss accounts for most cases of hypokalemic periodic paralysis. Neurology 2009;72:1544-1547.
19. Lin SH, Huang CL. Mechanism of thyrotoxic periodic paralysis. Journal of the American Society of Nephrology : JASN 2012;23:985-988.
20. Ramsay ID. Muscle dysfunction in hyperthyroidism. Lancet 1966;2:931-934.
21. Brody IA, Dudley AW, Jr. Thyrotoxic hypokalemic periodic paralysis. Muscle morphology and functional assay of sarcoplasmic reticulum. Archives

of neurology 1969;21:1-6.
22. Buruma OJ, Bots GT. Myopathy in familial hypokalaemic periodic paralysis independent of paralytic attacks. Acta neurologica Scandinavica 1978;57:171-179.
23. Links TP, Zwarts MJ, Wilmink JT, Molenaar WM, Oosterhuis HJ. Permanent muscle weakness in familial hypokalaemic periodic paralysis. Clinical, radiological and pathological aspects. Brain : a journal of neurology 1990;113 (Pt 6):1873-1889.
24. Van der Hoeven JH, Zwarts MJ, Van Weerden TW. Muscle fiber conduction velocity in amyotrophic lateral sclerosis and traumatic lesions of the plexus brachialis. Electroencephalography and clinical neurophysiology 1993;89:304-310.
25. Vogt TH, Fritz A. Computer-aided analysis of muscle fibre conduction velocity in neuromuscular diseases. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology 2006;27:51-57.
26. Kuwabara S, Kanai K, Sung JY, et al. Axonal hyperpolarization associated with acute hypokalemia: multiple excitability measurements as indicators of the membrane potential of human axons. Muscle & nerve 2002;26:283-287.
27. Inshasi JS, Jose VP, van der Merwe CA, Gledhill RF. Dysfunction of sensory nerves during attacks of hypokalemic periodic paralysis. Neuromuscular disorders : NMD 1999;9:227-231.
28. McComas AJ, Sica RE, McNabb AR, Goldberg WM, Upton AR. Evidence for reversible motoneurone dysfunction in thyrotoxicosis. Journal of neurology, neurosurgery, and psychiatry 1974;37:548-558.
29. Barroso FA, de la Fuente MI. Compound muscle action potential temporal dispersion during hypokalemia. Muscle & nerve 2009;40:662-663.

30. Bilodeau GM, Guderley H, Joanisse DR, Garland T, Jr. Reduction of type IIb myosin and IIB fibers in tibialis anterior muscle of mini-muscle mice from high-activity lines. Journal of experimental zoology Part A, Ecological genetics and physiology 2009;311:189-198.

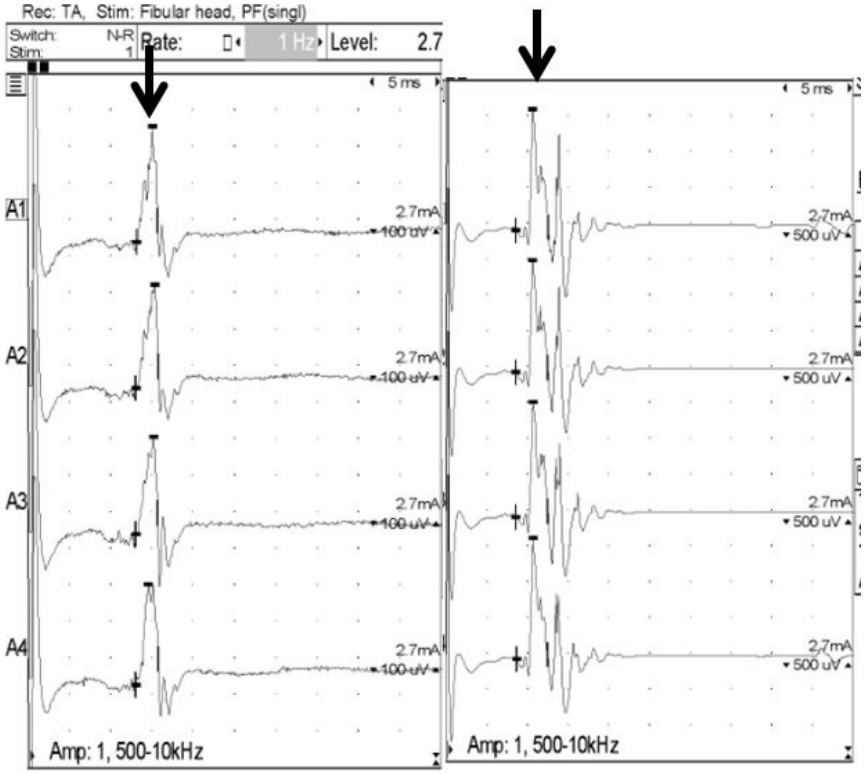

Figure 1. Examples of determination of MFCV.

Black arrow above trace indicate the peak latency needed to get the velocity.

Table 1. Clinical characteristics and muscle fiber conduction velocity (MFCV) measurements. In thyrotoxic periordic paralysis (TPP), values of the first MFCV test were presented. MFCVs in TPP seemed to be faster rather than delayed, compared with controls.

	control	TPP	P
Subjects, n	15	13	
Gender (F/M)	8/7	0/13	
Age, years (SD, ranges)	42.3 (14.1, 22-64)	35.9 (9.2, 25-59)	0.161
Days from attack, median, days (ranges)	-	7 (0-570)	
FT4, μg/dL (SD)		3.98 (0.75)	
TSH, median, μg/dL (ranges)		0.008 (0.001-7.230)	
K, mEq/L (SD)		3.98 (0.75)	
Positive PET (%)	0	9 (69.2)	
Fast MFCV, m/s (SD)	3.61 (0.58)	4.23 (0.58)	0.009
Slow MFCV, m/s (SD)	3.47 (0.34)	3.75 (0.63)	0.17
Mean MFCV, m/s (SD)	3.54 (0.40)	3.99 (0.53)	0.018
Fast / Slow ratio (SD)	1.00 (0.01)	1.14 (0.12)	0.002

Significant difference ($p < 0.05$).

PET, prolonged exercise test; MFCV, muscle fiber conduction velocity

Table 2. Serial muscle fiber conduction velocity (MFCV) measurements based on days from paralytic attack. MFCV measurements within 12 months from paralytic attack of thyrotoxic periodic paralysis (TPP) were faster compared with controls, while these differences disappeared after 12 months. This tendency was kept in comparing TPP and male control.

Category	Number of tests	Fastest MFCV, m/s, (SD)	Slowest MFCV, m/s (SD)	Mean MFCV, m/s, (SD)	Fast/Slow ratio (SD)	Age, year, (SD)	Positive PET, %	FT4, μg/dL, (% of hyperthyroidism)
Control	15	3.61 (0.58)	3.47 (0.34)	3.54 (0.40)	1.00 (0.01)	42.3 (14.1)		
Male control	8	3.83 (0.76)	3.55 (0.40)	3.69 (0.48)	1.00 (0.00)	39.7 (14.1)		
TPP								
Total	22	4.17 (0.60) [a, b]	3.70 (0.63)	3.91 (0.55) [a, b]	1.14 (0.13) [a, b]	37.7 (10.0)	74.1	2.51 (43.9)
<1 W	7	4.40(0.38) [a,b,c]	3.92(0.73)[c]	4.18(0.52) [a,b,c]	1.14(0.13) [a, b]	35.8(8.7)	80.0	3.00 (100)
1W-6 M	5	4.31(0.71) [a, b]	3.99(0.55) [a,b,c]	4.13(0.48) [a,b,c]	1.08(0.09)	40.1(9.5)	57.1	2.48 (57.1)
6-12 M	6	4.27(0.54) [a,c]	3.58(0.60)	3.84(0.50)	1.20(0.16) [a, b]	33.3(6.4)	85.7	2.64 (50)
>12 M	4	3.46(0.48)	3.13(0.14)	3.29(0.27)	1.11(0.27)	45.0(16.2)	75.0	1.29 (50)
≤12 M	19	4.33(0.51) [a,c]	3.83(0.63) [a,c]	4.05(0.50) [a,c]	1.15(0.14) [a, b]	36.5(8.5)	75.0	2.74 (72.7)

[a] Significant difference ($p < 0.05$) between control and TPP. [b] significant difference between male control and TPP. [C] significant difference compared with groups after 12 months from attack. MFCV, muscle fiber conduction velocity; TPP, thyrotoxic periordic paralysis; W, week from paralytic attack; M, months from paralytic attack; PET, prolonged exercise test

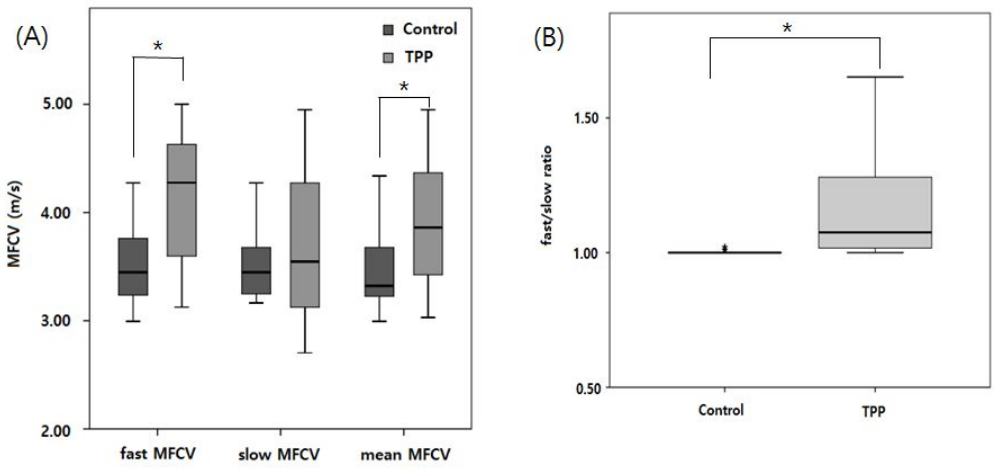

Figure 2. (A) Box-plots of fast (left), slow (middle) and mean (right) of Muscle fiber conduction velocity (MFCV) values in TPP and normal subjects, (B) Comparison of F/S ratio of MFCV. Note the significant differences for mean, fastest MFCV and the F/S ratio can be observed ($p < 0.01$).

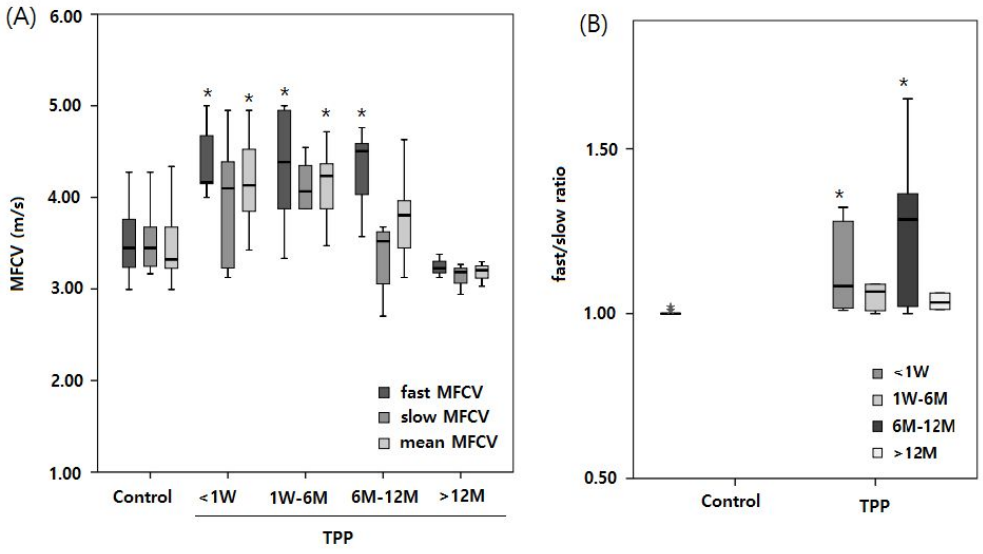

Figure 3. (A) Time dependent changes of muscle fiber conduction velocity (MFCV) measurements (B) Comparison of fast/slow ratio of MFCV. Note the significant difference in fastest MFCV between two groups within one year (* $p<0.05$) and higher F/S ratio in any time within one year compared to controls.

Table 3. Results of muscle fiber conduction velocity (MFCV) measurements based on prolonged exercise test (PET) and serologic tests. Positive PET group presented significantly faster MFCV than negative PET group. Other groups of abnormal serologic tests showed tendency of faster MFCV without significance.

	Number of tests	Fastest MFCV	Slowest MFCV	Mean MFCV	Fast/Slow ratio
Negative PET	20	3.75 (0.63)	3.50 (0.40)	3.61 (0.45)	1.04 (0.09)
Positive PET	17	4.17 (0.61)*	3.74 (0.66)	3.94 (0.56)	1.13 (0.14)*
Normal FT4	27	3.86 (0.67)	3.59 (0.49)	3.70 (0.51)	1.05 (0.10)
Abnormal FT4	10	4.14 (0.56)	3.64 (0.67)	3.91 (0.55)	1.15 (0.14)
Normal TSH	22	3.81 (0.67)	3.56 (0.46)	3.66 (0.48)	1.05 (0.11)
Abnormal TSH	14	4.10 (0.61)	3.68 (0.66)	3.90 (0.58)	1.13 (0.13)
Normal K	2	3.95 (0.65)	3.60 (0.54)	3.75 (0.52)	1.09 (0.15)
Abnormal K	34	4.42 (0.41)	3.81 (0.98)	4.18 (0.57)	1.18 (0.19)

* Significant difference ($p<o.o5$) between positive and negative PET groups

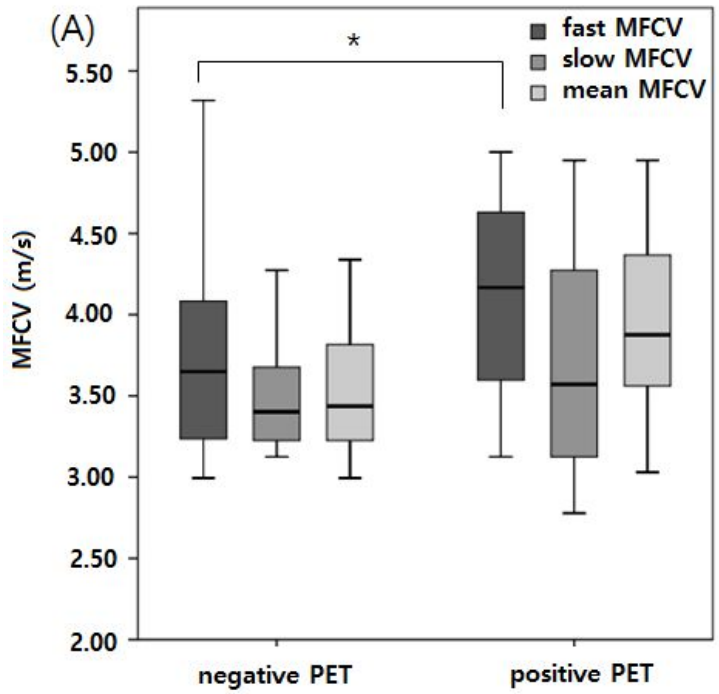

Figure 4. (A) Muscle fiber conduction velocity (MFCV) values depending on positivity of prolonged exercise test (PET) in thyrotoxic periodic paralysis (TPP). TPP patients with positive PET showed faster MFCV values than negative PET group.

국문초록

서론: 갑상선 중독 주기성 마비(Thyrotoxic periodic paralysis, 이하 TPP라 약함)는 갑상선 항진증과 관련되어 저칼륨혈증과 가역적인 이완성마비가 나타나는 질환이다. 임상적인 특성상, 골격근 세포막에서 이온 통로의 유전적 변이로 발생하는 저칼륨혈성 주기성 마비(hypokalemic periodic paralysis, 이하 familial HOPP라 약함)와 유사하나 TPP의 명확한 기전은 아직 밝혀지지 않았다. 본 연구는 근섬유 전도속도(MFCV)의 측정을 통해 TPP에서 근육막 수준의 이상이 있는지 살펴보고 가능한 기전을 유추해 보고자 하였다.

방법: TPP로 진단 받은 13명의 환자군과 15명의 대조군을 대상으로 임상 증상 및 증후, 신경전도검사, 장기운동유발검사(prolonged exercise tests, 이하 PET라 약함), 근섬유 전도속도(muscle fiber conduction velocity, 이하 MFCV라 약함)를 측정하였다.

결과: 환자군에서 MFCV는 지연되지 않았고, 증상발생 1년 이내에서는 통계적으로 유의하게 대조군과 비교하여 빠른 양상을 보였으며, 특히 PET 검사에서 양성인 경우에는 음성일때와 비교 하였을때 더 빠른 것으로 측정되었다. 혈액학적 검사나 호르몬의 변화는 MFCV의 결과에 통계적으로 유의한 영향을 미치지 않았으나, 증상발생으로부터의 시기, 몇 가지 감각신경전도검사에서의 결과들과는 역의 상관관계를 보였다.

결론: TPP는 임상적인 양상이 familial HOPP와 유사하더라도 MFCV를 촉진시키는 다른 기전이 있을 것으로 추측된다. 본 연구는 TPP가 신경의 흥분성과 같은 근섬유 활동전위의 전달을 촉진시키는 여러 요인들과 연관이 있음을 보여주며, 앞으로의 더 많은 연구가 필요하다.

주요어 : 갑상선 중독 주기성 마비, 근섬유 전도속도.

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