Exercise Test in the Inter-Attack Period of Thyrotoxic Periodic Paralysis: A Useful Diagnostic Tool

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Abstract- Exercise test was reported to be useful for some patients with periodic paralysis. We report here the results of exercise test in three cases of thyrotoxic periodic paralysis, for whom the exercise test was all positive. Exercise test could be one of the diagnostic tools in the "inter-attack" state of the probable cases with thyrotoxic periodic paralysis. However, the case number of this study is small and larger-scale studies may be warranted in the future.

Key Words: Exercise test, Thyrotoxic periodic paralysis

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INTRODUCTION

Provocative tests, such as oral glucose loading and intravenous glucose challenge tests, are considered to be helpful in the diagnosis of periodic paralysis (PP) in the inter-attack state[1]. However, these tests are time-consuming and require close monitoring of patients. The genetic analysis of calcium channel α1 subunit (*CACNA1S*), sodium channel 4A (*SCN4A*), potassium channel E3 (*KCNE3*), and potassium channel J2 (*KCNJ2*) may also be helpful in the diagnosis of primary hypokalemic periodic paralysis (HPP)[2]. However, these DNA-based diagnostic tools could be negative in patients with thyrotoxic periodic paralysis (TPP)[3-6], which was the most common etiology of hypokalemic paralysis in Taiwan[7]. The exercise test (ET) was considered useful in the diagnosis of periodic paralysis, especially in those cases related to channelopathy[8-14]. Also, positive ET has been documented in TPP cases[9,10,12,15-16]. Herein, we report the findings of inter-attack exercise test in three Taiwanese patients with TPP.

METHOD

Exercise test (ET)

In this study, ET was done according to the protocol reported before[8,17]. The supra-maximal compound muscle action potential (CMAP) at the abductor digiti minimi (ADM) muscle was recorded by stimulating the ulnar nerve at the wrist. The baseline-to-negative peak

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amplitude of each CMAP was measured. The CMAP was recorded once per minute for 5 minutes with the muscle at rest to ensure a stable baseline.

The patient performed maximal voluntary muscle contraction for 5 minutes (with relaxation for 3 to 4 seconds every 15 seconds). The ADM muscle was relaxed completely after the 5 minutes of exercise. CMAP was then recorded immediately thereafter every 2 minutes for 40 minutes or until the amplitude of the elicited CMAP no longer declined The percentages of increment and decrement were calculated. The exercise test was interpreted as a positive result when the decrement exceeded 40%[8]. The time needed to achieve 40% of decrement was also recorded.

Decrement was calculated as follows:

[(Highest amplitude after exercise - smallest amplitude after exercise)/Highest amplitude after exercise]×100%

Increment was calculated as follows:

[(Highest amplitude after exercise - amplitude before exercise)/amplitude before exercise]×100%

CASE REPORTS

Case 1

A 51-year-old man experienced an episode of general weakness of the four extremities on awakening in the morning. He could not get up from bed due to weakness. However, the weakness spontaneously resolved 11 hours later without medical intervention. Four similar attacks were noted in the following 5 days. The patient had a body weight loss of around 9 kg in the past 6 months. He also had a history of cigarettes smoking and betel nut chewing for more than 30 years. His family history was unremarkable. Physical examination showed a mildly enlarged thyroid gland and irregular heartbeats without murmur. Neurologic examination was unremarkable except for the wasting of bilateral thigh muscles, although muscle stretch reflex was normal and Gower's sign was negative. The patient's electrocardiogram (EKG) showed atrial fibrillation and moderate ventricular response. Technetium (Tc-99m) thyroid study scan showed diffusely increased amounts of the agent in the gland. The other laboratory data are listed in Table 1. Inter-attack electrophysiologic studies were performed. The results of motor nerve conduction, sensory nerve conduction, F responses, and H reflex studies were all within the reference limits. Repetitive nerve stimulation test was negative for decrementing response. Post-exercise facilitation was also negative. No myotonic discharge was found in electromyography. The results of ET are shown in Table 2 and Figure. The patient took oral propylthiouracil (PTU) 50mg twice daily for his hyperthyroidism and no more attacks of weakness was experienced thereafter.

Case 2

A 48-year-old man experienced an episode of weakness of bilateral lower extremities when he woke up at midnight. Significant soreness of both thighs and lower back was also noted at about the same time. At first, he could walk without dropping the slippers. The symptoms progressed and reached a nadir in the morning when he could no longer rise from bed. No sensory impairment, urine retention, slurred speech, difficulty in swallowing, double vision or blurred vision was found. Muscle strength recovered gradually and returned to normal 15 hours later, except for mild muscle soreness. A similar

Table 1. *Laboratory data of the three patients*

	K (meq/L)		CK	Free T4	T3	TSH	AMA	TBII
	Attack	Inter-attack	(U/L)	(ng/dL)	(ng/dL)	(uIU/mL)		(%)
Patient 1	2.5	4.2	30	3.66	207	< 0.2	1:400	50.8
Patient 2	ND	4.1	651	3.24	215	< 0.2	1:100	21
Patient 3	ND	3.9	53	10.13	260	< 0.2	1:25600	70

K: potassium; CK: creatine kinase (reference or normal range 15-130 U/L); free T4: free thyroxin T4 (reference 0.79-2.01 ng/dL); T3: triiodothyronine (reference 52-175 ng/dL); TSH: thyroid-stimulating hormone (reference 0.25-4 uIU/mL); AMA: Anti-microsomal antibodies (reference <1: 100); TBII: TSH-binding inhibitory immunoglobulins (reference <15%); ND: no data.

episode happened once before. No evidence of excessive exercise, work or a big meal was noted before this episode. There were symptoms of an upper respiratory tract infection one day before the attack. In reviewing his history, he had bilateral hand tremors in maintained posture 1 year before. Palpitation, heat intolerance, easy sweating, and insomnia were also noted in that period. His family history was unremarkable. Physical examination and neurologic examination were negative except for the postural and action tremors in both hands. The results of laboratory study were listed in Table 1. The inter-attack electrophysiologic studies were performed. The results of motor nerve conduction, sensory nerve conduction, F responses, and H reflex studies were all within the reference limits. No myotonic discharge was found in electromyography. The results of ET are shown in Table 2 and Fig.

Case 3

A 23-year-old man had the first episode of bilateral lower leg weakness when he was standing and playing online computer game two months ago. He fell down because of the weakness but the symptoms were completely resolved about 15 minutes later. However, such weakness happened several times in the past 2 months. Moreover, soreness and pain in bilateral thighs and lower back were also noted during these episodes of weakness. Physical examination showed mild enlargement of the thyroid gland. Neurologic examination was unremarkable except for action tremor. Technetium (Tc-99m) thyroid study scan showed diffusely increased agent in the gland. The laboratory data were listed in Table 1. Inter-attack electrophysiologic studies were performed. The results of motor nerve conduction, sensory nerve conduction, F responses, and H reflex studies were all within the reference limits. Repetitive nerve stimulation and post-exercise facilitation tests were both negative. No myotonic discharge was found in electromyography. The patient took oral methimazole 10mg three times a day for the hyperthyroidism. No more attacks of weakness were found during the admission. The results of ET are shown in Table 2 and Fig.

Table 2. *Results of the exercise test in the three patients*

	Patients		
	1	2	3
CMAPs (before exercise, mV)	8.9	8.4	8.3
CMAPs (immediately after exercise, mV)	9.6	9.6	9.9
CMAPs (after exercise, lowest, mV)	5.1	4.2	3.1
Time to nadir (minutes)	22	42	48
Recording time (after exercise, minutes)	40	46	48
Increment (%)	7.9	14.3	19.3
Decrement (%)	46.9	56	68.7
Time to 40% decrement (minutes)	18	26	24

CMAPs: compound muscle action potentials

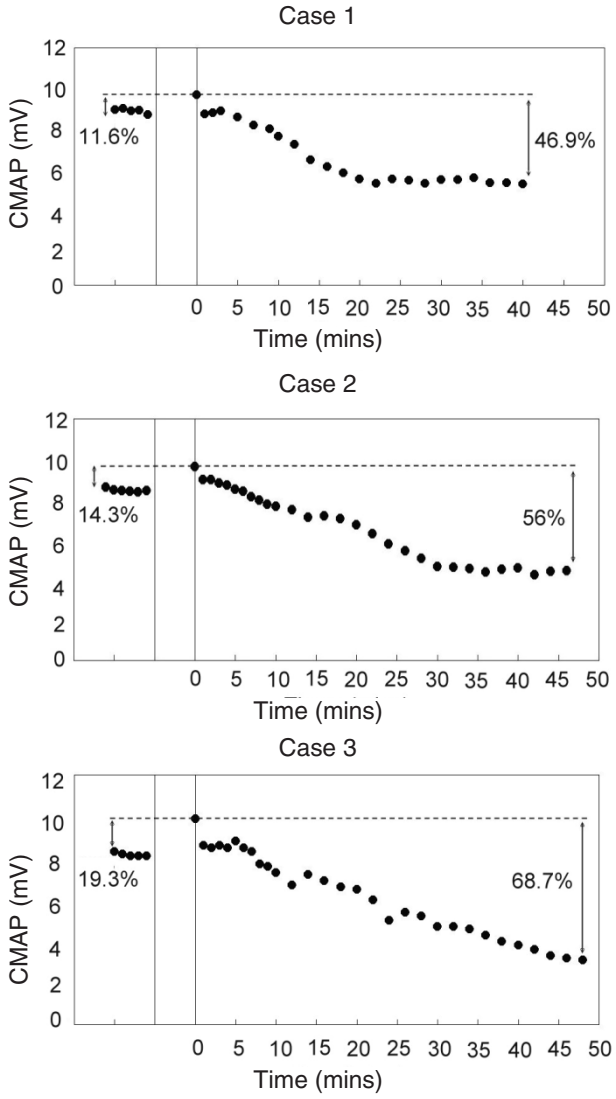

Figure. The results of exercise test in the three patients

RESULTS

Patient 1-3 showed a significant increase in the amplitude of CMAPs immediately after the exercise. All of the three patients showed a progressive decline in CMAP amplitude after the exercise and the decrements were all greater than the cutoff value of 40% (46.9%, 56%, and 68.7% for patients 1 to 3, respectively). The time needed to exceed a 40% decrement was 18, 26, and 24 minutes, and the time needed to nadir was 22, 42, and 48 minutes, for patient 1, 2, and 3, respectively, The results of ET are shown in Table 2 and are plotted in Figure.

DISCUSSION

The characteristic presentations of ET include a progressive decline in CMAP amplitude after the exercise with or without an increase in CMAP amplitude immediately after the exercise. The ET is considered to be "positive" only if there is more than a 40% decrement[8]. With these criteria, positive ET results are rarely found in healthy individuals[8,9,12-14]. In previous studies[8-14], positive ET was mostly found in patients with primary PP for unknown reasons.

The 5-minute exercise might be considered as a provocative factor of attack in primary PP patients. The increment of CMAP potentials immediately after exercise is considered as an increase in muscle membrane excitability, whereas the progressive decrement after the exercise is probably related to a decrease in membrane excitability[14]. Positive ET in TPP may suggest an abnormal excitability of the muscle membrane and relatively easy induction of paralytic attacks under slightly low potassium conditions[12]. In this study all 3 patients with TPP showed positive result of ET.

Most of the previous studies showed significant decrement in ET in the primary periodic paralysis and TPP[8-16]. The finding of CMAP potential increment immediately after exercise was not so consistent as the finding of progressive decrement after exercise. Patients with primary hyperkalemic periodic paralysis were reported to have a more significant increment than those with primary hypokalemic periodic paralysis, although they all showed a decrement in the subsequent test[13].

In ET study, there are 5 electrophysiologic patterns in previous reports[13]. The electrophysiologic findings of primary hyperkalemic periodic paralysis (T704M sodium channel mutation) and hypokalemic periodic paralysis (R528H calcium channel mutation) were classified as pattern IV (increment/ decrement) and pattern V (normal/ decrement), respectively[13]. To our knowledge, there is no definite cut-off value to define the criteria of incremental changes in the previous reports. In this study, all of the three patients with TPP had incremental responses (7.9%, 14.3%, and 19.3%, respectively).

The different degrees of incremental response immediately after exercise in HPP might suggest a heterogeneous finding in TPP patients. A high incidence of positive decremental responses was also noted in the other reports of TPP patients[9,10,12,15,16]. Shift from a positive decrement response in ET to a negative decrement response after treatment of hyperthyroidism was also noted in previous studies[9,16]. In the study of secondary non-thyrotoxic periodic paralysis[10,12,18], 2 patients with Anderson syndrome had positive ET, which became negative after treatment[18].

In conclusion, ET can be positive, although not specific, for different types of periodic paralysis. Further biochemical studies are needed to confirm the subtype of periodic paralysis. However, ET is a non-invasive procedure that may be a useful electrophysiologic method in monitoring the disease status of TPP or even the other types of PP. ET can also be one of the diagnostic tools in the "inter-attack" state of patients with clinically probable periodic paralysis. However, the case number of this study is small and larger-scale studies may be warranted in the future.

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