



Evaluation and validation of sustained upgaze combined with the ice-pack test for ocular myasthenia gravis in Asians

Hyun Joo Kee^a, Hee Kyung Yang^{a,*}, Jeong-Min Hwang^a, Kyung Seok Park^b

^a Department of Ophthalmology, Seoul National University College of Medicine, Seoul National University Bundang Hospital, 82, Gumi-ro 173beon-gil, Bundang-gu, Seongnam, Gyeonggi-do, South Korea

^b Department of Neurology, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Gyeonggi-do, South Korea

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Abstract

The accuracy of the ice-pack test for diagnosing myasthenia gravis (MG) has been reported to be excellent, however, the sensitivity is low in patients with mild ptosis which is common in Asians who have absent or low double eyelid folds. Herein, we performed the ice-pack test after sustained upgaze and tested its validity for diagnosing MG. The study included 30 newly diagnosed MG patients with ptosis (median age 47 years, range 2–87 years) and 30 controls with ptosis other than MG (median age 58 years, range 5–83 years). All MG patients initially presented with ptosis and/or diplopia; 26 patients had purely ocular MG while 4 patients progressed to generalized MG. All patients performed the new ice-pack test after sustained upgaze for 2 min. The ice-pack test was judged positive if there was an improvement of at least 2 mm of margin reflex distance compared to the level of ptosis before (conventional ice-pack test) or after (new ice-pack test) sustained upgaze. Subgroup analysis was performed according to the level of ptosis. The conventional test showed 43.3% sensitivity and 100% specificity for diagnosing MG, while the new ice-pack test achieved 73.3% sensitivity and 96.7% specificity, respectively. In patients with mild ptosis, the sensitivity and specificity for diagnosing MG were 27.8% and 100% by the conventional test, and 72.2% and 96.7% by the new ice-pack test, respectively. The new ice-pack test combined with sustained upgaze was more sensitive for diagnosing MG, particularly in patients with mild ptosis which is common in Asians.

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1. Introduction

Myasthenia gravis (MG) is an autoimmune disorder with antibodies targeted to acetylcholine receptors (AChRs) in the postsynaptic membrane [1]. Impaired neuromuscular junction transmission results in weakness of skeletal muscles [1]. Diagnostic tests for MG include single fiber electromyography [2], repetitive nerve stimulation test [3], anti-acetylcholine receptor antibody (AChR-Ab) assay [4], rest test [5], ice-pack test [6], sleep test [7], and Tensilon[®] or neostigmine test

[8]. In patients with negative AChR-Ab, antibodies against muscle-specific kinase (MuSK), low-density lipoprotein receptor-related protein 4 (LRP4), cortactin, or agrin could be helpful for the diagnosis of MG [9]. However, there is no single gold standard test for diagnosing ocular myasthenia that has both good sensitivity and specificity [10]. The sensitivity and specificity of the ice-pack test for diagnosing ocular myasthenia have been reported to be excellent [11–13]. In contrast, our prior study showed that the sensitivity of the ice-pack test was relatively low when patients with mild ptosis were included, and the diagnostic yield improved only after repeated tests [6]. This is particularly important in the evaluation of Asians who have absent double eyelid folds or lower height of folds compared to Caucasians. As a result, the absolute amount of eyelid drooping may be less prominent in Asians with myasthenic ptosis [14,15].

* Corresponding author.

E-mail address: eye@snuh.org (H.K. Yang).

Fatigability is one of the hallmarks of MG [16], thus inducing fatigue before performing the ice-pack test may increase the sensitivity of the test, particularly in patients with subtle or mild ptosis. Therefore, in this study, we induced fatigue by sustained upgaze before performing the ice-pack test in the evaluation of myasthenia gravis, and determined the validity of the new ice-pack test in patients with variable level of ptosis.

2. Materials and methods

2.1. Participants

We performed a retrospective study on patients with ptosis, 30 newly diagnosed MG patients and 30 control patients with other causes of ptosis, who presented at Seoul National University Bundang Hospital between 2013 and 2017. Among the patients with MG, 26 had purely ocular MG and 4 patients progressed to generalized MG during follow-up examinations. All participants had unilateral or bilateral ptosis with a margin reflex distance (MRD) of less than 3.0 mm. MG was diagnosed by a history of ptosis and/or diplopia with diurnal variation, and a positive test result of at least one of the followings; serum AChR-Ab test, repetitive nerve stimulation test, or neostigmine test. As for the control group, 24 patients had aponeurotic blepharoptosis and 6 patients had ptosis related to oculomotor nerve palsy. Patients who were not able to perform the ice-pack test were excluded. Institutional Review Board approval was obtained before data collection. All clinical investigation was conducted according to the principles of the Declaration of Helsinki.

Subgroup analysis was performed according to the level of ptosis before performing the ice-pack test. Among patients with MG, 12 patients had moderate to severe ptosis with a pretest MRD of <0 mm, and 18 patients had mild ptosis with a pretest MRD of ≥ 0 mm.

2.2. Ice-pack test with fatigue induction by sustained upgaze

All tests were performed before receiving any medical treatment. The ice-pack test was performed after fatigue induction by looking far above as much as possible for 2 min. MRD was measured 3 times; (1) before sustained upgaze (MRDa), (2) immediately after sustained upgaze (MRDb), and (3) after applying an ice pack on both eyelids for 2 min (MRDc). Full face photographs were taken with a 5-mm sticker on the patients' forehead for standardization of image size. MRD was measured on standard photographs with a millimeter ruler as the distance between the center of the pupillary light reflex and the upper eyelid margin with the eye in primary gaze. The examiner (HJK) was blinded to the patients' clinical status. The ice-pack test was defined positive if there was an improvement of MRD by 2 mm or more after the ice-pack test [17]. In patients with bilateral ptosis, the data of only one eye with more severe ptosis was included [6].

2.3. Main outcome measures

Primary outcomes were (1) change in MRD after fatigue induction (MRDb-a), (2) improvement in MRD after the conventional ice-pack test (MRDc-a), and (3) improvement in MRD after the new ice-pack test after sustained upgaze (MRDc-b). The results were compared between MG patients and controls using the independent *t*-test, χ^2 test or Mann-Whitney U test (SPSS software, version 22, SPSS, Inc.). Sensitivity and specificity of fatigue induction, conventional ice-pack test and new ice-pack test for diagnosing MG were also determined. A *P* value of <0.05 was considered statistically significant.

3. Results

3.1. Patients

The clinical characteristics of the MG group and controls are presented in Table 1. There were no significant differences in baseline characteristics including the pretest MRD between MG patients and controls.

3.2. Diagnostic value of fatigue induction with sustained upgaze

Change in MRD after sustained upgaze (MRDb-a) was -1.6 ± 1.7 mm (range, -7.8 to 0.0) in the MG group, and -0.4 ± 0.6 mm (range, -1.7 to 0.4) in controls. The amount of eyelid drooping after sustained upgaze was significantly larger in patients with MG compared to controls ($P = 0.002$) (Table 1).

Validity of fatigue induction according to variable cutoff values of the change in MRD after sustained upgaze were determined. With a cutoff value of MRDb-a ≤ -1.5 mm, the sensitivity and specificity for diagnosing MG were 36.7% and 96.7%, respectively. With a cutoff value of MRDb-a ≤ -1.0 mm, sensitivity and specificity for diagnosing MG were 46.7% and 80.0%. With a cutoff value of MRDb-a ≤ -0.5 mm, the sensitivity and specificity were 73.3% and 60.0%, respectively.

3.3. Diagnostic value of the new ice-pack test with fatigue induction

After the conventional ice-pack test, improvement of MRD (MRDc-a) was 1.9 ± 1.8 mm (range, 0.0 to 9.3) in the MG group and -0.4 ± 1.3 mm (range, -5.0 to 1.6) in controls, which was significantly larger in the MG group ($P < 0.001$) (Table 1).

After the new ice-pack test with fatigue induction by sustained upgaze, improvement of MRD (MRDc-b) was 3.5 ± 2.3 mm (range, 1.0 to 10.3) in the MG group and 0.0 ± 1.0 mm (range, -3.7 to 2.1) in controls, which was significantly larger in the MG group ($P < 0.001$).

The conventional ice-pack test showed a sensitivity and specificity of 43.3% and 100%, respectively, for diagnosing

Table 1
Clinical characteristics of patients with ptosis related to myasthenia gravis and controls.

	Myasthenia gravis (n = 30)	Control (n = 30)	P value
Age (years)	46.6 ± 24.0 (range 2–87, median 47)	53.0 ± 20.7 (range 5–83, median 58)	0.275 ^a
Female gender	14 (46.7%)	16 (53.3%)	0.606 ^b
AChR-Ab positive	23 (76.7%)		
Jolly test positive	19 (63.3%)		
Treatment			
Pyr	15 (50.0%)		
Pred ± Pyr	7 (23.3%)		
AZA ± Pred/Pyr	5 (16.7%)		
Thymectomy	6 (20.0%)		
Pretest MRD (mm)	−0.2 ± 1.7 (−4.4 to 2.2)	−0.3 ± 2.3 (−5.4 to 2.5)	0.853 ^c
ΔMRD after sustained upgaze (mm)	−1.6 ± 1.7 (−7.8 to 0.0)	−0.4 ± 0.6 (−1.7 to 0.4)	0.002 ^c
ΔMRD after conventional ice-pack test (mm)	1.9 ± 1.8 (0.0 to 9.3)	−0.4 ± 1.3 (−5.0 to 1.6)	<0.001 ^c
ΔMRD after new ice-pack test (mm)	3.5 ± 2.3 (1.0 to 10.3)	0.0 ± 1.0 (−3.7 to 2.1)	<0.001 ^a

Mean ± SD (range), AChR-Ab = Anti-acetylcholine receptor antibody, AZA = azathioprine, Pred = Prednisone, Pyr = Pyridostigmine Bromide, MRD = margin reflex distance.

^a Independent *t*-test.

^b χ^2 test.

^c Mann–Whitney U test.

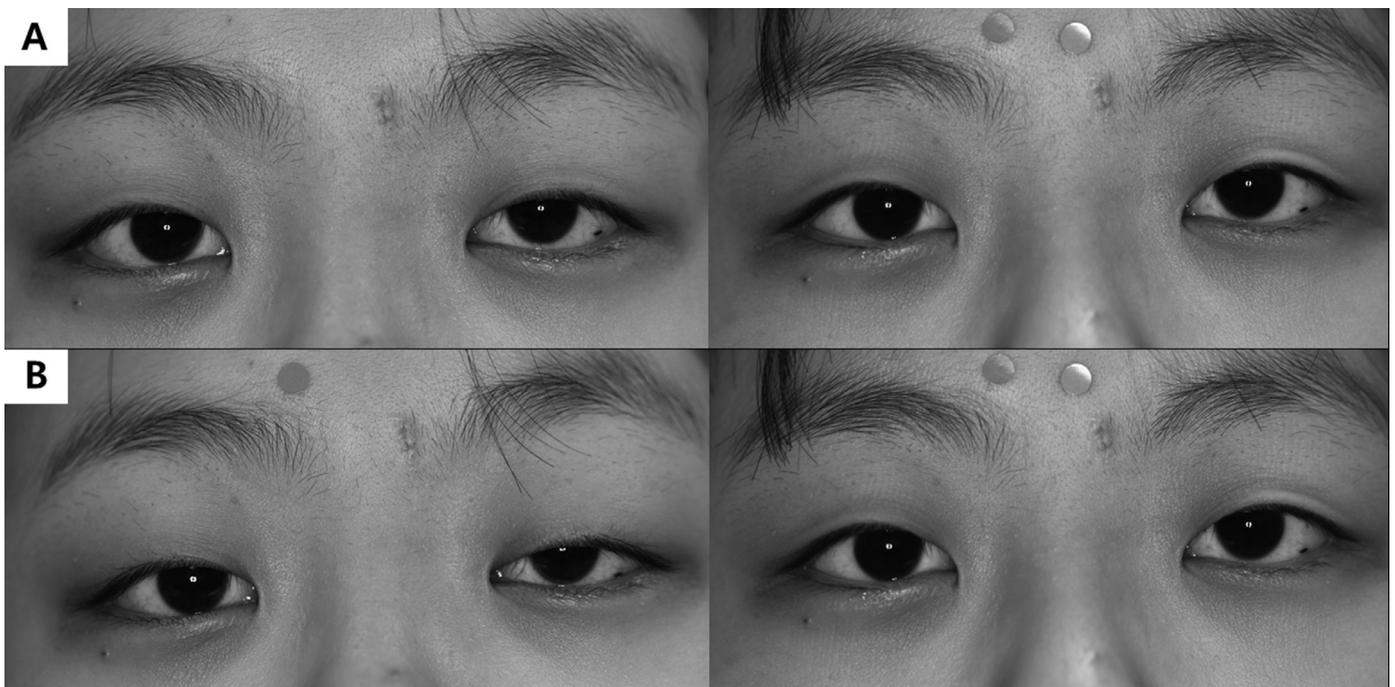


Fig. 1. A case with ocular myasthenia gravis confirmed by positive serum anti-acetylcholine receptor antibody and repetitive nerve stimulation test. A. (Left) Pretest photograph shows a margin reflex distance (MRD) of 1 mm in the left eye (OS). (Right) After applying an ice-pack on both eyelids for two minutes, the change in MRD was 1.7 mm OS showing a negative result with the conventional ice-pack test. B. (Left) Pretest photograph after sustained upgaze showing an MRD of 0 mm OS. (Right) After applying an ice-pack on both eyelids for two minutes, the change in MRD was 2.7 mm OS showing a positive result with the new ice-pack test combined with fatigue induction.

MG. The new ice-pack test with fatigue induction after sustained upgaze showed 73.3% sensitivity and 96.7% specificity. The sensitivity of the new ice-pack test with fatigue induction was 30% higher than the conventional ice-pack test.

Fig. 1 shows a case with ocular myasthenia gravis confirmed by positive AChR-Ab and repetitive nerve stimulation test. Ptosis was mild with a pretest MRD of

1 mm in the left eye. The conventional ice-pack test showed a negative result, while the new ice-pack test performed after sustained upgaze showed a positive result.

3.4. Subgroup analyses

Subgroup analysis was performed according to the pretest MRD. There were no significant differences between the two

Table 2
Clinical characteristics of patients with myasthenia gravis according to the degree of ptosis.

	Moderate to severe ptosis (n=12)	Mild ptosis (n=18)	P value
Age(years)	45.5±28.5	47.3±21.2	0.586 ^a
Female	5 (41.7%)	9 (50.0%)	0.654 ^b
AChR-Ab positive	9 (75.0%)	14 (77.8%)	1.000 ^a
Jolly test positive	7 (58.3%)	12 (66.7%)	0.712 ^a
ΔMRD after sustained upgaze (mm)	-0.8±0.8 (-2.6 to 0.0)	-2.1±1.9 (-7.8 to 0.0)	0.017 ^c
ΔMRD after conventional ice-pack test (mm)	2.9±2.2 (1.1 to 9.3)	1.2±1.0 (0.0 to 3.2)	0.003 ^c
ΔMRD after new ice-pack test (mm)	3.7±2.3 (1.4 to 10.1)	3.3±2.4(1.0 to 10.3)	0.415 ^c

Mean ± SD (range), AChR-Ab = Anti-acetylcholine receptor antibody, MRD = margin reflex distance.

^a Fisher's exact test.

^b Independent *t*-test.

^c Mann-Whitney U test.

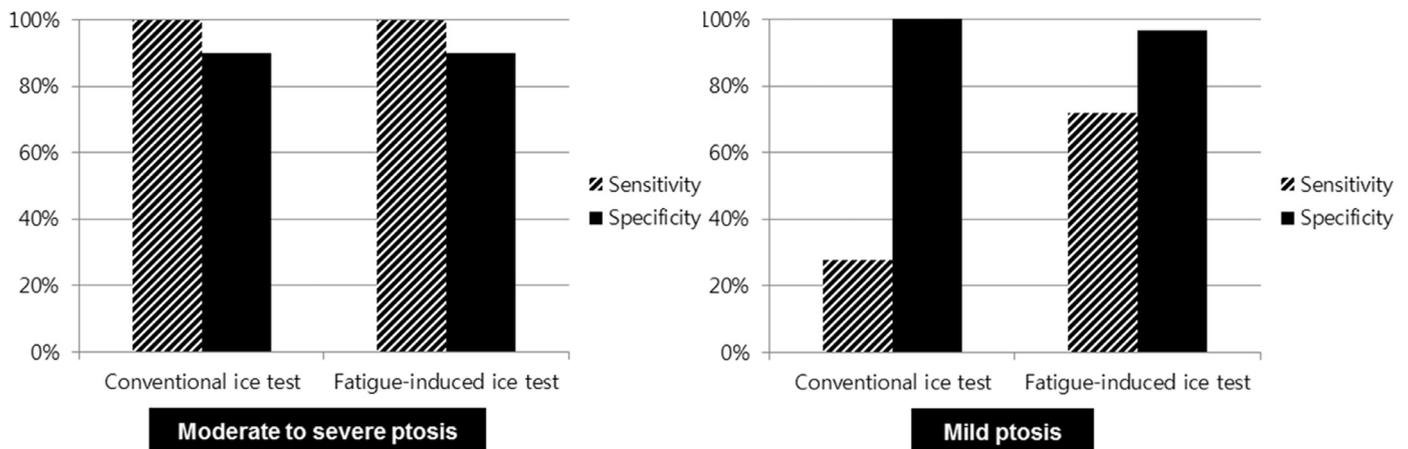


Fig. 2. Validity of the ice-pack test for diagnosing ocular myasthenia gravis (MG) according to the level of ptosis. (Left) In patients with moderate to severe ptosis, the sensitivity and specificity for diagnosing MG were 100% and 90%, respectively, by both the conventional and new ice-pack test. (Right) In patients with mild ptosis, the sensitivity and specificity for diagnosing MG were 27.8% and 100% by the conventional ice-pack test, respectively, and 72.2% and 96.7% by the new ice-pack test with fatigue induction.

groups in terms of age, sex, positive responses to AChR-Ab assay and the repetitive nerve stimulation test, respectively (Table 2).

After sustained upgaze, the change in MRD (MRDb-a) was -0.8 ± 0.8 mm (range, -2.6 to 0.0) in moderate to severe ptosis, and -2.1 ± 1.9 mm (range, -7.8 to 0.0) in mild ptosis, showing significantly more drooping of eyelids after fatigue induction in patients with mild ptosis ($P=0.017$).

Improvement of MRD after the conventional ice-pack test without sustained upgaze (MRDc-a) was 2.9 ± 2.2 mm (range, 1.1 to 9.3) in moderate to severe ptosis, and 1.2 ± 1.0 mm (range, 0.0 to 3.2) in mild ptosis, which was significantly smaller in patients with mild ptosis ($P=0.003$).

Improvement of MRD after the new ice-pack test with sustained upgaze (MRDc-b) was 3.7 ± 2.3 mm (range, 1.4 to 10.1) in moderate to severe ptosis, and 3.3 ± 2.4 mm (range, 1.0 to 10.3) in mild ptosis, which was not significantly different ($P=0.415$).

In patients with moderate to severe ptosis, the sensitivity and specificity for diagnosing MG were 90% and 100%, respectively, by both the conventional and the new ice-pack test with fatigue induction (Fig. 2).

In patients with mild ptosis, the sensitivity and specificity for diagnosing MG were 27.8% and 100% by the conventional ice-pack test, respectively, and 72.2% and 96.7% by the new ice-pack test with fatigue induction (Fig. 2).

4. Discussion

This study demonstrated the efficacy of fatigue induction in diagnosing MG together with the new ice-pack test which was performed after fatigue induction by sustained upgaze. The new ice-pack test with fatigue induction achieved higher sensitivity compared to the conventional test, particularly in patients with mild ptosis. In addition, 1.5 mm or more drooping of eyelids after fatigue induction was highly specific for diagnosing ocular MG, although the sensitivity was relatively low.

In our study, the sample size was larger than most of the previous reports regarding the diagnostic accuracy of the ice-pack test in MG [5,11,13,17–19]. Fatigue induction before performing the ice-pack test raised the sensitivity from 43.3% to 73.3%, which is comparable to repeated test results showing a sensitivity of 73.1% [6]. In our prior

study, repeated tests increased the sensitivity of the ice-pack test compared to a single test [6]. The present study was performed in extension from the prior study to increase the accuracy of the ice-pack test in patients with subtle or mild ptosis. We found that the sensitivity of the ice-pack test could be substantially improved by inducing fatigue before performing the test, which is much more efficient than repeating tests on another day which is time-consuming. Thus, inducing fatigue with sustained upgaze before performing the ice-pack test is a convenient and efficient method to reduce the chance of false negative results in diagnosing MG, particularly in cases with mild or subtle ptosis. This is particularly notable in Asians who have an absent or low eyelid crease compared to Caucasians, in which the absolute amount of MRD change may be less prominent in MG [14].

Previous studies have reported high diagnostic accuracy of the ice-pack test with sensitivities of 80–95% and specificities of 79–100% for diagnosing MG [5,18–20]. However, in our study, the sensitivity of the conventional ice-pack test was only 43.3%, which is similar to our previous report [6]. One of the reasons for this difference is the variable level of ptosis in MG patients before performing the ice-pack test [6]. The study by Golnik and colleagues included MG patients with at least 2 mm of ptosis [18], and the pretest palpebral fissure size ranged from 0 to 8 mm with an average value of 4 mm. Our study included MG patients with a pretest MRD ranging from –4 to +2 mm and a mean value of 0 mm. Regarding the level of pretest ptosis, Golnik et al. [18] reported false negative ice-pack test results in 3 out of 4 MG patients with complete ptosis, and concluded that the sensitivity of the ice-pack test was low in patients with complete ptosis. Such cases with complete ptosis were not included in our study. In our study, we found that the sensitivity and specificity of the ice-pack test for diagnosing MG may differ according to the level of ptosis. Specifically, the sensitivity of the ice-pack test increased after fatigue induction only in patients with subtle or mild ptosis, whereas in those with moderate to severe ptosis, there was no significant change with fatigue induction.

Fatigability with drooping eyelids is the hallmark symptom of MG, however, there is no definite criteria for determining fatigability of eyelids after sustained upgaze. Mittal et al. [21] reported that 80% of 83 MG patients showed positive fatigability on sustained upgaze, however, they did not mention any specific numerative criteria. In this study, a cutoff value of 1.5 mm or more drooping of eyelids after sustained upgaze was highly specific (96.7%) for diagnosing MG, although the sensitivity was relatively low (36.7%). Among MG patients, the amount of eyelid drooping after sustained upgaze was larger in patients with mild ptosis compared to those with moderate to severe ptosis. On the other hand, 26.7% of MG patients showed less than 0.5 mm of eyelid drooping after fatigue induction, which suggests that fatigability is variable and depends on the condition of the patient at the time of the test. Fatigable ptosis has also been reported in various diseases such as angiocentric T cell lymphoma with lymphomatoid vasculitis [22], paraneoplastic

syndrome [23], Chiari type I malformation [24], adult-onset Leigh syndrome [25], dorsal midbrain glioma [26], Lambert-Eaton myasthenic syndrome [27], and RYR1-related congenital myopathy, however, there has been no report of the ice-pack test results in any of these diseases [28,29]. Therefore, fatigability alone is not specific nor sensitive enough for the diagnosis of MG.

There are some limitations in this study that should be mentioned. First, this study was retrospective with only a limited number of patients included. The control group consisted of mainly aponeurotic blepharoptosis and oculomotor nerve palsy. Thus, inclusion of other causes of ptosis such as eyelid edema, inflammation or demyelinating diseases may affect the accuracy of the test. Second, as our institution is a tertiary hospital, the sensitivity and specificity might be different from those of the general MG population. Further controlled prospective studies may be necessary to better understand the validity and limitations of the ice-pack test in diverse situations. Finally, fatigue induction was incorporated in the middle of the conventional ice-pack test, which might affect the results of the conventional test as muscles were fatigued through prolonged upgaze. However, in our previous study, we found that negative results of the ice-pack test was frequently found in ocular MG patients with mild ptosis, and the sensitivity of the conventional ice-pack test without fatigue induction (38.5–53.8%) was similar to the results of the conventional ice-pack test in our present study (43.3%) [6].

In conclusion, performing the ice-pack test after fatigue induction by sustained upgaze increases the sensitivity of the test, especially in patients with mild or subtle ptosis related to MG which is common in Asians with ocular MG.

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