안과학 석사학위논문

안검하수를 동반한 중증근무력증에서 반복된 Ice Test의 진단적 가치

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서울대학교 대학원

의학과 안과학

박 준 영

Abstract

TITLE: Diagnostic Value of Repeated Ice Tests in the Evaluation of Ptosis in Myasthenia Gravis

PURPOSE: To determine the repeatability and diagnostic value of the ice test in the evaluation of ptosis in myasthenia gravis (MG).

DESIGN: Retrospective review.

METHODS: Twenty-six patients with ptosis related to MG and 38 controls with ptosis other than MG were included. All patients were tested with the ice test 2 times on separate days in the afternoon. The margin reflex distance (MRD) was measured before and immediately after 2-minute application of ice on the eyelids. The ice test was judged positive if there was an improvement of at least 2.0 mm MRD after the ice test. 'Equivocal'was defined by improvement of MRD from at least 1.0 mm to less than 2.0 mm after the ice test.

RESULTS: Repeated ice tests showed an agreement of 61.5% in MG, and 97.4% in nonmyasthenic ptosis. Repeated ice tests increased the positive predictive

value by 2.7%, the negative predictive value by 11.6% and sensitivity by 26.9% compared to a single test. Among the patients with repeatedly negative test results, 63.7% of those who showed equivocal results at least once turned out to be MG. Of those with repeated non-equivocal negative results, nobody turned out to be MG. There was no statistically significant difference of the results of the ice test between ocular MG and generalized MG ($p = 0.562$).

CONCLUSIONS: The repeatability of the ice test was 61.5% in myasthenic ptosis. Repeated ice tests enhanced the sensitivity of the test by 27% compared to a single test. Patients with an equivocal negative result had a 64% chance to have MG.

Contents

Introduction:

Myasthenia gravis (MG) is a neuromuscular disorder caused by impaired synaptic transmission across the neuromuscular junction owing to acquired autoimmunity to the motor endplate, resulting in decreased available acetylcholine receptors (AChRs).[1] Half of myasthenic patients initially present with ocular involvement.[2] Patients with MG commonly have ophthalmologic symptoms and signs including ptosis, diplopia, and ophthalmoplegia.[3,4] These manifestations may be variable to the point of being absent during an isolated examination.

Diagnostic tests for MG can be performed in the office including the ice test[3], sleep test[5], rest test[6], antiacetylcholine receptor antibody (AchR-Ab) assay[7], Jolly test (electromyography with repetitive nerve stimulation)[8], neostigmine test[9,10] and antimyasthenic regimen trial[10]. However, none of these tests are 100% sensitive or specific.[11]

Previous studies have reported that ice test has a sensitivity of 90-95% and a specificity of 100%.[3,6,12] The major advantages of the ice test are its simple and noninvasive nature, short test duration and that no specialized equipment or trained personnel are required.[13] However, little is known of the repeatability of the ice test in myasthenic ptosis and controls. Herein, we report the results of the

repeatability of the ice test in the evaluation of ptosis in MG.

Methods:

Participants

Twenty-six patients with ptosis related to MG and 38 controls with ptosis other than MG were included. All patients had at least 2 mm of ptosis and were studied between January 2012 and February 2014 at the neuro-ophthalmology clinic of Seoul National University Bundang Hospital (SNUBH). Patients with MG were diagnosed by an obvious history of diurnal variation and/or fatigue and a positive result of at least one of the followings; AchR-Ab assay, neostigmine test, Jolly test, antimyasthenic regimen trial.[10] As for the control group, 38 patients with ptosis due to involutional blepharoptosis, oculomotor nerve palsy, thyroid associated ophthalmopathy, Miller-Fisher syndrome, congenital blepharoptosis, Horner's syndrome, chronic progressive external ophth-almoplegia and oculomotor nerve palsy due to internal carotid artery aneurysm were included. We obtained Institutional Review Board (IRB) approval from SNUBH before data collection (The SNUBH IRB No. B-1504-296-112). The research conducted met the tenets of Helsinki.

Ice test

All patients were tested with the ice test 2 times on separate days in the

afternoon. The margin reflex distance (MRD) was measured before and immediately after 2-minute application of ice on the eyelids. MRD was defined as the distance between the center of the pupillary light reflex and the upper eyelid margin with the eye in primary gaze. All measurements were made with a millimeter ruler to the nearest 0.5 mm. The ice test was positive if there was an improvement of at least 2.0 mm MRD after the ice test (Fig 1).[14] In case of a negative ice test result, 'Equivocal' was defined by improvement of MRD from at least 1.0 mm to less than 2.0 mm after the ice test. Results of repeated ice tests were judged by the maximum change in fissure size after the ice tests.

Main outcome measures

The primary outcome was the repeatability of the ice test performed on separate days. The diagnostic value of the ice test including positive predictive value, negative predictive value, sensitivity, and specificity were also compared between repeated tests. Ice test results were compared using the t test, χ^2test or Fisher's exact test (SPSS software, version 15, SPSS, Inc.). A p value less than 0.05 was considered significant for all statistical tests.

Results:

Patient Demographics and Baseline Characteristics

In the MG group, there were 14 (53.8%) women and 12 (46.2%) men. Ages ranged from 3 to 77 years (mean 39.5 ± 23.5 years). In the control group, there were 18 (47.3%) women and 20 (52.7%) men without MG. Ages ranged from 3 to 75 years (mean 35.2 ± 25.1 years) (Table 1).

Repeatability of the ice test

Repeated ice tests showed an agreement in 61.5% (16 of 26) of patients with MG, and 97.4% (37 of 38) of controls.

Diagnostic value of the ice test

The two separate test results were considered as independent cases. After a single ice test, 24 of 52 (46.2%) cases with MG and 2 of 76 cases (2.6%) without MG showed a positive test result ($P < 0.001$, Fisher's exact test). The positive predictive value was 92.3% (24 of 26), negative predictive value was 72.5% (74 of 102), sensitivity was 46.2% (24 of 52), and specificity was 97.4% (74 of 76) (Table 2).

After repeated ice tests, 19 of 26 (73.1%) patients with MG and 1 of 38

patients (2.6%) without MG showed a positive test result at least once ($P < 0.001$, Fisher's exact test). The positive predictive value was 95.0% (19 of 20), negative predictive value was 84.1% (37 of 44), sensitivity was 73.1% (19 of 26), and specificity was 97.4% (37 of 38) (Table 3). Repeated ice tests increased the positive predictive value by 2.7%, the negative predictive value by 11.6% and sensitivity by 26.9% compared to a single test.

Among the patients with repeatedly negative test results, 63.7% (7 of 11) of those who showed equivocal results at least once turned out to be MG. Of those with repeated non-equivocal negative results, 0.0% (0 of 33) turned out to be MG.

MG patients were subgrouped into ocular MG and generalized MG according to their association with systemic manifestations. However, there was no statistically significant difference in the results of the ice test between the two subgroups ($p = 0.562$, χ^2test).

The variability of ptosis before application of the ice test (pre-test MRD) was determined of the repeated tests. The mean variability of the pre-test MRD was 0.56±0.53 (range, 0-2) in patients with MG and 0.25±0.35 (range, 0-1) in controls, which was significantly larger in patients with MG ($p < 0.001$, independent t-test).

After the ice test, there were no side effects except for mild local discomfort of the eyelids in all patients.

Discussion:

This is the first study reporting the repeatability of the ice test in the evaluation of ptosis in myasthenia gravis. Furthermore, there is a significant difference between our results and previous studies in regard of the 1) diagnostic value of the ice test and 2) interpretation of 'equivocal' results of the ice test.

A majority of patients with MG have a history of diurnal variation and/or fatigue. Ocular manifestations in MG may be variable, from severe ptosis and/or diplopia to the point of being absent during an isolated examination.[15] Because of such characteristics, the ice test demonstrated poor repeatability in MG (61.5%) compared to non-myasthenic ptosis (97.4%) in our study. As the symptoms of MG usually aggravate during the evening, we had all patients take the test in the afternoon. Nevertheless, there was a distinct difference in the results of the ice test performed on different days. Although the repeatability of the ice test (61.5%) in MG was relatively poor in our study, repeated tests may enhance the validity of the ice test. Our study showed that repeated ice tests increased the positive predictive value by 2.7%, the negative predictive value by 11.6% and sensitivity by 26.9% compared to a single test.

The diagnostic value of the ice test in previous studies was reported to show a sensitivity of 90-95% and a specificity of 100%.[3,6,12] In contrast, the

accuracy of a single ice test was much lower in our study, showing a sensitivity of 46.2% and specificity of 97.4%. Repeated ice tests increased the sensitivity to 73.1% and specificity to 97.4%. One of the reasons for this difference may be caused by the variable degree of ptosis on different days in patients with MG. That is, the degree of ptosis prior to the ice test (pre-test MRD) may be variable, as shown in our study. Previous studies have not dealt with such characteristics of MG. In cases of MG with complete ptosis, it is known that the ice test may show negative results.[3] However, even patients with complete ptosis may show variable degree of ptosis during the day.[15] In addition, the sample size of our study was larger than the previous studies, and owing to the variable degree of ptosis on different days and time of day, we speculate that this may have affected the test results, which partly explains the low sensitivity of a single ice test, and increased sensitivity with repeated tests. An additional step to induce sufficient fatigue before the ice test may be beneficial to acquire more reliable results in the diagnosis of MG. There was no statistically significant difference in the results of the ice test between ocular MG and generalized MG, unlike the anti-acetylcholine receptor antibody which the positive rate is much higher in generalized MG.[16]

In our study, negative results were subdivided into 'equivocal' and 'non

equivocal' negative results. Among the patients with repeated negative results, 63.7% of patients who showed an equivocal negative result at least once turned out to have MG, but otherwise no patient had MG. In other words, a patient showing non-equivocal negative results repeatedly may have a very low chance of having MG. Conversely, if a patient showed an equivocal result of 1-2mm improvement, the possibility of having MG would be 64%, and a strong suspicion of MG would be reasonable. If the ice test was judged positive when improvement of MRD was ≥ 1.0 mm at least once after repeated tests, the sensitivity is 100% (26 of 26) and specificity is 81.5% (31 of 38) (Table 3). This increases the sensitivity by 26.9%, while a decrease in specificity by 15.9% occurs compared to the original criteria. If the ice test was judged positive when improvement of MRD was ≥ 1.5 mm at least once after repeated tests, the sensitivity is 88.4% (23 of 26) and specificity is 84.2% (32 of 38).This increases the sensitivity by 15.3%, while a small decrease in specificity by 13.2% occurs compared to the original criteria. Therefore, if the ice test should be used as a screening test of MG, equivocal negative results should be interpreted as 'possible MG', despite the small increase in false positive rates this might cause. Our study shows that the clinical significance of the ice test in terms of the interpretation of negative results, either equivocal negative or non-equivocal

negative, may be important in the diagnosis of MG. In our study, cases that showed false positive results of the ice test included Miller-Fisher syndrome and ptosis secondary to internal carotid artery aneurysm. Cases showing equivocal negative results except MG included ischemic oculomotor nerve palsy with ptosis and thyroid associated ophthalmopathy. As ptosis is rare in thyroid associated ophthalmopathy and MG is more frequent in patients with thyroid disease,[17,18] an equivocal negative result of the ice test may imply a‘possible MG’even if other test results are all negative for MG, and close observation for the symptoms of MG would be necessary.

The limitations of our study are that it was a retrospective one, and there could have been a selection bias towards patients with more variable symptoms and good compliance to repeated examinations. In addition, 12 patients in the MG group were taking acetylcholinesterase inhibitors prior to the ice test. However, a previous study reported that patients taking acetylcholinesterase inhibitors at the time of the ice test still had positive responses, and thus medications did not have to be stopped.[3] We verified that there was no statistically significant difference of the positive rates (58.3% vs 85.7%) and equivocal negative rates (41.7% vs 14.3%) of the ice test between MG patients taking anti-cholinesterase inhibitors before the test and those who

did not ($p = 0.116$, χ^2test). Further well controlled researches to investigate the factors causing different results of the ice test may be helpful, particularly the degree of ptosis before the test. It would also be beneficial to ascertain the usefulness of inducing fatigue as an additional step before the ice test.

In conclusion, the repeatability of the ice test was 61.5% in myasthenic ptosis. Repeated tests enhanced the sensitivity of the test by 26.9% compared to a single test. Equivocal negative results should be interpreted with caution, as these patients have a possibility to have MG in 63.7%.

Figure:

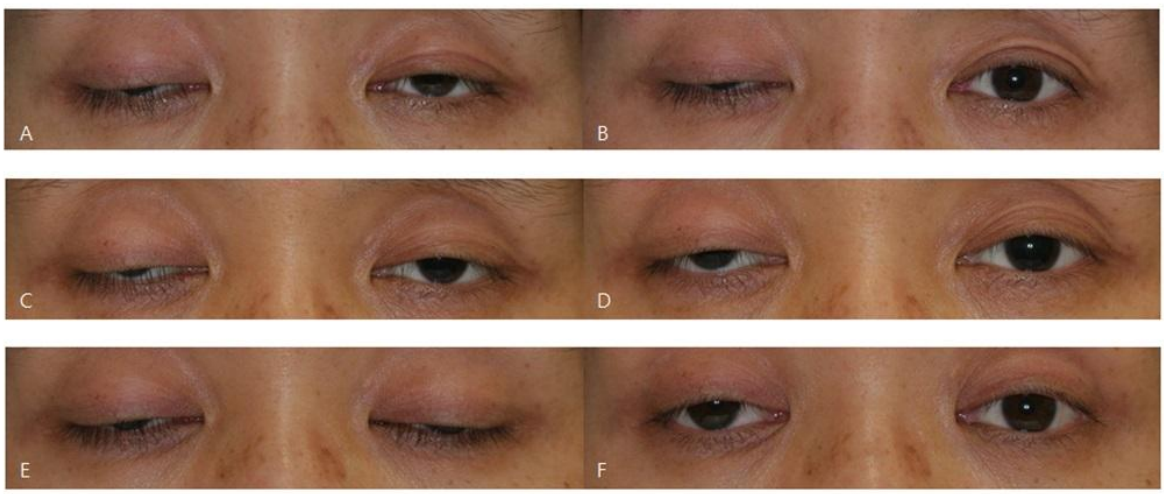

FIGURE1. A patient with ptosis of both eyes with myasthenia gravis, showing inconsistent results of the ice test performed on separate days in the right eye. (A) Asymmetric ptosis was present in both eyes prior to the ice test. (B) Immediately after 2-minute ice application, ptosis in the left eye significantly improved with a fissure change of 2.5 mm. In contrast, the right eye showed a negative result. (C) Ptosis of both eyes in the same patient on a different day prior to the ice test. (D) After the ice test, ptosis in the right eye improved with a fissure change of 1.0 mm, showing an equivocal negative response. (E) Ptosis of both eyes in the same patient on a different day prior to the ice test. (F) After the test, right eye ptosis improved with a fissure change of 2.0 mm, showing a positive result.

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

	Myasthenia gravis	Control	p value
Number	26	38	
Age(yrs)	39.46 ± 23.47	35.23 ± 25.07	0.510†
Female gender	14 (53.8%)	18 (42.3%)	0.611‡
Anti-AchR Antibody titer			
Positive	10 (38.5%)		
Negative	16 (61.5%)		
Jolly test			
Positive	9 (34.6%)		
Negative	17 (65.4%)		
Neostigmine test			
Positive	5 (19.2%)		
Negative	13 (50.0%)		
Not tested	8 (30.8%)		
Treatment			
Pyr	11 (45.5%)		
Pyr/Pred	8 (30.8%)		
AZP	1 (3.8%)		

AZP/Pred	1 (3.8%)		
Change in fissure (mm)	1.88 ± 1.27 (0-4.0)	0.23 ± 0.84 (-1.5-3)	<0.001†

*Data are means ± SD (minimum-maximum)

*AChR = Acetylcholine receptor, Pyr = Pyridostigmine Bromide, Pred = Prednisolone, AZP = Azathioprine

*†T-test, ‡χ^2test

Table 2. The results of a single ice test

	Diagnosis		Total
	MG	Control	
Ice test*			
Positive	27	2	29
Negative	35	74	109
Equivocal	22	6	
Non-equivocal	13	68	
Total	62	76	138

MG = Myasthenia gravis

*The ice test was positive if there was an improvement of at least 2.0 mm in MRD after the ice test. In case of a negative test result, equivocal was defined as an improvement in MRD of at least 1.0 mm to less than 2.0 mm after the ice test.

Table 3. The results of repeated ice tests

	Diagnosis		Total
	MG	Control	
Ice test*			
Positive	20	1	21
Negative	11	37	48
Equivocal	10	4	
Non-equivocal	1	33	
Total	31	38	69

MG = Myasthenia gravis

*Repeated ice test results were considered positive if there was a positive test result at least once. When both test results were negative, equivocal was judged if there was an equivocal result at least once

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Abstract in Korean (국문 요약):

제목: 안검하수를 동반한 중증근무력증에서 반복된 ice test의 진단적 가치

목적: 중증근무력증에서 안검하수를 평가하는 방법 중 ice test의 재현성 및 진단적 가치에 대해 규명하고자 한다.

연구 설계: 후향적 전자의무기록 검토 및 분석

방법: 2012년도 1월부터 2014년도 2월까지 분당서울대병원 신경안과 외래에 내원한 2 mm이상의 안검하수가 있는 환자 중 중증근무력증 환자군 26명 52안, 중증근무력증 이외의 원인으로 발생한 안검하수를 가진 대조군 38명 76안이 포함되었다. Ice test를 각기 다른 날 오후에 2회 시행한 안검하수를 동반한 중증근무력증 환자군과 대조군에서 ice test 시행 전, 후 각막의 빛 반사점으로부터 상안검연 중앙부까지의 거리를 측정하여 2 mm 이상 호전될 경우 양성, 2 mm 미만으로 호전될 경우 음성으로 평가한 후 두 군간의 ice test의 재현성 및 민감도, 특이도, 양성예측도, 음성예측도를 포함한 진단적 가치에 대해 비교한다. Ice test의 결과가 음성인 경우 중 호전 정도가 1 mm 이상 2 mm 미만일 경우는 'equivocal' 로 정의하였다.

결과: 반복된 ice test의 결과간의 일치도는 중증근무력증 환자군에서 61.5%,

대조군에서 97.4%를 보였다. 반복된 ice test는 단일 ice test와 비교하여 양성예측도는 2.7%, 음성예측되는 11.6%, 민감도는 26.9% 증가하였다. 반복적으로 음성 결과를 보인 환자에서 2번의 결과 중 한번 이상 equivocal을 보인 경우 63.7%가 중증근무력증으로 판명되었다. 반복적으로 equivocal이 아닌 음성으로 결과를 보인 환자들은 중증근무력증이 아무도 없었다. 눈에 국한된 중증근무력증과 전신 중증근무력증 사이에서 ice test의 결과는 통계학적으로 유의한 차이를 보이지 않았다. (p = 0.562).

결론: 안검하수를 가진 중증근무력증에서 반복된 ice test의 결과간의 일치도는 61.5%이다. 반복된 ice test는 단일 ice test와 비교하여 민감도를 27% 높일 수 있다. Ice test 결과가 음성을 보인 환자에서 equivocal에 해당한 경우는 64%에서 중증근무력증일 가능성이 있다.