

# The Ice Pack Test in the Differential Diagnosis of Myasthenic Diplopia

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**Purpose:** To investigate the diagnostic value and to establish threshold criteria for the ice pack test as an office preliminary test in the differential diagnosis of myasthenic diplopia in comparison with blepharoptosis.

**Design:** Prospective, comparative cohort study.

**Participants:** Eighty-nine patients with a recent onset of diplopia, blepharoptosis, or both were evaluated with orbital cooling in a prospective manner. Forty-eight patients presented with diplopia, 25 patients with both blepharoptosis and ophthalmoplegia and 16 patients with blepharoptosis.

**Testing:** All patients had the ice pack applied for 5 minutes on both eyelids at the initial orthoptic evaluation. Increasing the duration of cooling to 10 minutes was investigated in 36 diplopic patients. A complete diagnostic work-up was ordered and patients were followed up for a minimum of 6 months before diagnosis of myasthenia gravis was ascertained.

**Main Outcome Measures:** Difference in cover test measurements in primary position or marginal reflex distance before and after the application of the ice pack, specific cause for diplopia and blepharoptosis.

**Results:** Fifteen patients were diagnosed as myasthenic. The optimal cutoff point for a positive response to the ice pack test proved to be a reduction in ocular deviation in primary position by 50% or by 10 prism diopters (PD) or more for presenting deviations larger than 20 PD. By this criterion, sensitivity for the detection of myasthenic diplopia was 76.9% (95% confidence interval [CI], 49.06%–92.50%) for the 5-minute application, compared with 92.3% (95% CI, 63.5%–98.9%) sensitivity demonstrated for blepharoptosis. Increasing the time of application to 10 minutes did not improve the diagnostic value of the test. Specificity was high (98.3%; 95% CI, 90.3%–99.9%) and was demonstrated even in patients with coexisting myasthenic and dysthyroid ophthalmopathy. Patients with oculomotor nerve paresis and Horner syndrome invariably were nonresponsive to the test.

**Conclusions:** The ice pack test demonstrated high specificity and an acceptable sensitivity in the differential diagnosis of myasthenic diplopia. Data from this series suggest that a partial rather than a complete response to the ice pack test may be expected for myasthenic diplopia. Standardization of the method of application of the ice pack is critical for the interpretation of its effect.

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The differential diagnosis of acquired strabismus is broad, including parietic strabismus, myasthenia gravis, and other myopathic disorders such as restrictive strabismus and chronic progressive external ophthalmoplegia. Depending on its cause, diplopia may represent an ominous sign stemming from a central nervous system tumor or aneurysm or a transient self-limiting manifestation of microvascular angiopathy.

Myasthenia gravis is an often underdiagnosed<sup>1</sup> cause for diplopia and ptosis. Although variability and fatigability are the clinical hallmarks of this disorder, establishing the diagnosis involves paraclinical testing with more or less promptly accessible tests such as acetylcholine receptor antibodies, repetitive nerve stimulation, single-fiber electromyography, and the edrophonium test. Simple clinical tests that can be performed in the office such as the rest test, the sleep test, and the more recently described ice test would be of great value in orienting the differential diagnosis and may minimize costly neuroimaging referrals.

The ice test, involving orbital cooling through the application of ice over closed eyelids, has been proposed as a reliable clinical test for the diagnosis of ocular myasthenia gravis.<sup>2</sup> Its specificity reportedly reaches 100%, with a sensitivity of 80%, in the evaluation of myasthenic blepharoptosis.<sup>3,4</sup> The diagnostic value of this test in the differential diagnosis of diplopia,<sup>5</sup> however, is less well established.<sup>6,7</sup>

In the single published study focusing on extraocular muscle responses,<sup>5</sup> the authors reported 100% sensitivity and a dramatic improvement in alignment with the application of the ice pack. However, in a subsequent review<sup>8</sup> the test is referred to as not well-studied for ophthalmoparesis. According to the authors, it usually is used for the evaluation of ptosis rather than ophthalmoparesis.

This study was carried out to address the diagnostic validity of the ice pack test in the evaluation of diplopia of potential myasthenic cause and to establish a cutoff point for a positive response. The test was applied also to patients

with blepharoptosis (isolated or combined with diplopia) to test the prevailing, yet unproven, hypothesis that this is not as good a test for diplopia as for blepharoptosis. The effect of increasing the time of application of the ice pack as well as its diagnostic value when more than one ocular motility disorders coexist was investigated as well.

## Patients and Methods

One hundred two patients seeking treatment at the Orthoptic Clinic conducted by one of the authors (KIC) from June 2005 through September 2006 were evaluated with orbital cooling in a prospective manner. Subjects were enrolled among consecutive patients with diplopia, ptosis, or both at presentation. Inclusion criteria were a recent (less than 1 month) onset or unclear cause of symptoms. Patients were excluded when there was a reliable history suggesting the presence of restrictive strabismus such as orbital fracture associated diplopia or an infectious inflammatory cause for blepharoptosis or if follow-up time was fewer than 6 months. A battery of diagnostic tests, as specified below, was ordered, and a minimum follow-up time of 6 months was required before diplopia or blepharoptosis was confirmed to be assigned to a specific cause.

The primary outcome measures were the change in the strabismic deviation induced by the ice pack application (quantitated as outlined in detail below) and specific diagnostic entities for ophthalmoparesis. At the conclusion of the study, myasthenic patients were compared with controls (patients with nonmyasthenic acquired ocular motility disorders, ptosis, or both) in terms of response to orbital cooling. Secondary outcome measure was the change in marginal reflex distance (MRD) induced by the ice pack application and specific diagnostic entities for blepharoptosis. Sensitivity and specificity of the test for diplopia and ptosis were determined based on these data. The study met the requirements of the local institutional review board for approval. Informed consent was obtained by patients submitted to both the 5- and 10-minute application trial.

The ice test was applied at the initial evaluation of the patients in the Orthoptic Clinic. The assessment of ocular deviation, ptosis, or both in primary position was performed and recorded immediately before and after the application of the ice pack by an independent observer, masked to the patient's history and differential diagnostic considerations. A thin surgical glove filled with ice was applied against the closed lids of a seated patient. The ice pack was held in place by the patient, who was advised to hold it firmly against the eyelids without excessive pressure. In rare instances, the patient was assisted in holding the ice pack, if it was determined that arm fatigue may compromise cooperation. Care was taken so that the surface configuration of the ice pack would correspond directly to the contour of the eyelids.

The ice pack was applied routinely on both eyes for 5 minutes. For 36 diplopic patients, a titration of the time of application of the test was performed by applying the test for 5 and 10 minutes on distinct time points on the same day separated by 1 hour at least.

The ice pack was applied bilaterally in patients with diplopia and those with diplopia and blepharoptosis. As a rule, patients with blepharoptosis had the ice pack applied over both eyelids, regardless of the apparent unilaterality of the clinical situation. Only on the occasional instance of a patient with eyelid retraction in one eye and ptosis in the other eye was the ice pack applied unilaterally.

A detailed history was elicited as to the method of onset of diplopia, variability in the clinical picture (diplopia worse in the evening as opposed to awakening), and associated symptoms, such

as severe headache. A detailed systemic history was obtained including administration of medication, the presence of microvascular systemic disease (diabetes mellitus, hypertension), thyroid dysfunction, and the possibility of autoimmune vasculitis. A detailed ophthalmic history to rule out the possibility of preexisting strabismus was obtained as well.

A complete ophthalmologic examination was undertaken, including best-corrected visual acuity, testing for anisocoria, slit-lamp examination of the anterior segment looking for nonspecific signs of inflammation, eversion of the eyelids to rule out the presence of inflammatory conjunctivitis, applanation tonometry, and funduscopy.

Evaluation of patients with ptosis was made by recording the MRD with a millimeter ruler to the nearest 0.5 mm, immediately before and after applying the ice pack. The influence of the frontalis muscle was eliminated by applying digital pressure on the muscle. To ensure that MRD evaluation was carried out on the fixating eye, the contralateral eye was occluded. Thus, the possibility of pseudoptosis in the nonfixating hypotropic eye of patients with coexisting strabismus and ptosis was eliminated. The clinical diagnosis of Horner syndrome was confirmed by reversal of anisocoria after the instillation of apraclonidine 1% drops in both eyes.<sup>9</sup>

Orthoptic evaluation of diplopia included assessment of ocular motility, alternate prism and cover test measurements in the cardinal positions of gaze, and recording of the presence and type of compensatory head position. Assessment of fusion and stereopsis was obtained especially in cases where decompensation of preexisting phorias or microtropia was suspected. Forced duction testing in the office was performed to rule out restrictive strabismus in selected patients. Additional work-up included a complete blood count, Westergren erythrocyte sedimentation rate, fasting glucose and glycosylated hemoglobin, urea, creatinine, antinuclear antibodies, and additional tests on an individual basis.

Acetylcholine receptor (AChR) antibodies and, when negative, muscle-specific kinase (MuSK) antibodies were determined in 62 patients suspected to be myasthenic. They were not ordered routinely when the clinical picture was highly suggestive of a paretic cause (such as posttraumatic onset) that was confirmed by subsequent complete resolution of symptoms.

The neostigmine (Prostigmin; ICN Pharmaceuticals, Costa Mesa, CA) test was administered in patients with a high index of suspicion for myasthenia, especially when acetylcholine receptor antibody testing proved negative. The interpretation of the results of the neostigmine test was supported by the opinion of the evaluating neurologist.

The reference standard for the diagnosis of myasthenia was a positive result in the anti-AChR or anti-MuSK testing, positive neostigmine test results, or a combination thereof. For selected patients with a high diagnostic index of suspicion for myasthenia and negative or equivocal results in the above tests, a therapeutic antimyasthenic regimen trial was initiated. Whenever the diagnosis was based solely on positive neostigmine test results, it was verified by subsequent clinical course and therapeutic responses to the myasthenic treatment regimen. Furthermore, a minimum follow-up of 6 months was required before establishment of the diagnosis.

The diagnosis of ocular versus generalized myasthenia was based on reports from the last follow-up examination. The diagnosis of chronic progressive external ophthalmoplegia was based on positive muscle biopsy for ragged-red fibers.

For patients older than 60 years with acquired constant diplopia, obvious incomitance, and predisposing vasculopathic parameters that improved within 3 to 4 months of follow-up, the neostigmine test was not offered routinely. A brain computer tomographic scan nevertheless was obtained in 50 of 73 diplopic patients and magnetic resonance imaging of the brain, orbit, or both, was

obtained in 22 patients, 11 patients having undergone both computer tomographic and magnetic resonance imaging examinations.

The diagnostic criterion for positive results in the evaluation of diplopia initially was defined as a reduction by at least 50% in the angle of deviation (in at least 1 of the components, horizontal or vertical), obtained with alternate prism and cover test measurements in primary position after the application of the ice pack. After the diagnostic work-up of diplopia was completed, the data were analyzed to optimize a cutoff point for a positive response (see "Results" and "Discussion").

For patients evaluated for blepharoptosis, the threshold for a positive response to the test was an increase of 2 mm or more in the MRD measurements after the application of the ice pack.<sup>4</sup> When bilateral but asymmetric ptosis was encountered, improvement by 2.00 mm or more in at least 1 eye was considered a positive result. Statistical analysis included descriptive statistics of involved parameters and determination of sensitivity and specificity.

## Results

Eighty-nine patients, 56 males and 33 females aged 27 to 83 years (mean, 54 years), were included in the study and form the basis of this report. Thirteen patients were excluded because of loss to follow-up before establishment of diagnosis, history of posttraumatic restrictive strabismus, or inflammatory cause for blepharoptosis. Mean follow-up time was 9.3 months (range, 6–30 months). No adverse effects to the application of the ice pack, except for mild to moderate discomfort within the first 2 minutes of application, were noted in any of these patients.

Positive neostigmine test results were obtained in 5 of 28 patients tested. Among 62 patients submitted to serologic antibody testing, 9 had positive results for the acetylcholine receptor antibodies and 1 had positive results for MuSK.

Overall, 15 patients were diagnosed with myasthenia gravis, and 74 patients diagnosed with other entities served as controls. Seventy-three patients (13 myasthenic and 60 controls) were tested for ophthalmoparesis (diplopia) and 41 patients (13 myasthenic and 28 controls) were tested for blepharoptosis. Twenty-five of these patients (11 myasthenic and 14 controls) had both diplopia and blepharoptosis and were tested concurrently for these 2 conditions. Sensitivity and specificity of the ice pack test were calculated in the total population of patients tested for each condition, diplopia (n = 73) or blepharoptosis (n = 41).

Schematically, the patients can be divided into 3 groups according to the presenting symptomatology: group 1 comprises 48 patients with isolated diplopia, 2 of whom were diagnosed as myasthenic, 33 with parietic strabismus (6 with oculomotor, 16 with trochlear, and 11 with abducens nerve palsy), and 13 with diplopia of miscellaneous cause, including 4 patients with a recent onset of diplopia bearing the diagnosis of Graves' disease, 2 cases of decompensated intermittent exotropia (convergence insufficiency type), 2 patients with decompensated microtropia, and 1 case each of divergence insufficiency, late-onset comitant esotropia, skew deviation, fixation switch diplopia, and diplopia after cataract surgery.

Group 2 comprises 25 patients with both diplopia and blepharoptosis: 11 were diagnosed as myasthenic, 8 with oculomotor nerve palsy, 4 with chronic progressive external ophthalmoplegia, 1 patient with recurrent Tolosa-Hunt syndrome, and 1 patient with coexisting levator dehiscence and diplopia after cataract surgery.

Group 3 comprises 16 patients with isolated ptosis at presentation: 2 were diagnosed as myasthenic, 4 with Horner syndrome, and 10 with miscellaneous causes of ptosis, including levator dehiscence (n = 6) and congenital (n = 2) and contact lens-related (n = 2) blepharoptosis.

Table 1. Results of the Ice Pack Testing in Myasthenic versus Nonmyasthenic (Main Diagnostic Entities) Patients

	Positive* Ice Test Results	Negative Ice Test Results	Total
Myasthenia gravis (n = 15)			
Ophthalmoplegia	10	3	13
Blepharoptosis	12	1	13
Any of the above	14 <sup>†</sup>	4 <sup>‡</sup>	15
Nonmyasthenic patients (n = 74)			
Ophthalmoplegia	1	59	60
Paretic strabismus	1	40	41
IIIrd nerve <sup>§</sup>	0	14	14
IVth nerve <sup>§</sup>	1	15	16
Vth nerve <sup>§</sup>	0	11	11
CPEO	0 <sup>  </sup>	4	4
Miscellaneous	0	15	15
Blepharoptosis	2	26	28
IIIrd nerve palsy	0	8	8
Horner syndrome	0	4	4
CPEO	0 <sup>  </sup>	4	4
Miscellaneous	2	18	20
Any of the above	3 <sup>†</sup>	71 <sup>‡</sup>	74

CPEO = chronic progressive external ophthalmoplegia.

\*Positivity by the lower threshold criterion of 50% reduction in deviation in primary position or at least 10 prism diopters for deviations or 25 prism diopters or more.

<sup>†</sup>Positive for either diplopia or blepharoptosis (at least one), whichever was present in each patient.

<sup>‡</sup>Negative ice test response for diplopia and blepharoptosis.

<sup>§</sup>Paresis or paralysis.

<sup>||</sup>Partial response as evidenced by a decrease in deviation by 25% was noted in 3 of 4 patients, and an elevation of the upper eyelid by 1 to 1.50 mm was noted in all 4 patients.

The results of the ice pack test in myasthenic versus nonmyasthenic patients is summarized in Table 1. The results of the ice pack test (5-minute application on initial presentation) were positive in 9 of 73 patients with diplopia, 8 of whom subsequently were identified as myasthenic and 1 of whom was diagnosed with fourth-nerve paresis (specificity, 98.3%; 95% confidence interval [CI], 90.3%–99.9%). The latter patient is a 71-year-old female with 6 prism diopters (PD) of right hyper-tropia compatible with right fourth-nerve paresis after herpes zoster ophthalmicus. The positive effect of the ice test was transient, lasting for less than 1 minute. A thorough work-up, including a brain computed tomographic scan, AchR and MuSK antibodies, antinuclear antibodies, and fluorescent treponemal antibody-absorption (FTA-ABS), were negative. C-reactive protein was elevated (30 mg/l; reference range, <5 mg/l). Diplopia resolved within 6 weeks and was attributed to inflammatory fourth-nerve paresis.

The ice pack test results were positive in 15 of 41 patients with ptosis, 13 of whom were identified as myasthenic. In the sample of patients with nonmyasthenic ptosis, the test results proved to be false positives in 2 of 29 patients (specificity, 93.1%; 95% CI, 76.9%–99.1%). The first patient is a 39-year-old woman who also had diplopia and a history of recurrent attacks of painful ophthalmoplegia attributed to orbital myositis at presentation, and the second patient carried the diagnosis of common pemphigi. The neostigmine test and acetylcholine receptor antibodies analysis showed negative results in these patients. The ice pack test did not improve coexisting ocular misalignment in the former patient. A therapeutic trial of anti-

cholinesterase medication (pyridostigmine) did not improve diplopia or ptosis in either patient.

Table 2 presents the clinical characteristics and results of diagnostic tests for 15 patients subsequently diagnosed as myasthenic. Thirteen (86.6%) of 15 myasthenic patients reported diplopia. Eight of these patients responded positively to the 5-minute test on initial evaluation by diminished primary position deviation of at least 50% (sensitivity, 61.5%; 95% CI, 35.4%–82.4%). One patient who had a partial response not fulfilling the 50% improvement criterion responded positively when the ice pack was applied for 10 minutes (sensitivity for the 10-minute application, 69.2%; 95% CI, 42.0%–87.6%).

Three patients subsequently diagnosed as myasthenic had a recent diagnosis of thyroid eye disease at presentation (patients 13, 14, and 15, Table 2; Fig 1). Excluding these 3 patients from analysis, the sensitivity of the ice test for diplopia would be 70% (7 of 10 patients tested; 95% CI, 39.23%–89.67%).

Three patients (patients 11, 13, and 14, Table 2) were tested on several occasions with variable angles of deviation before treatment of myasthenia was initiated. One patient (patient 14) initially had a deviation of 40 PD extropia (XT) and a clinical picture of bilateral pseudointernuclear ophthalmoplegia that was not responsive to the application of the ice pack for either 5 or 10 minutes at presentation. Subsequent presentation a few days later with 10 PD of extropia promptly reversed with application of the ice pack for 5 minutes.

Deviations larger than 20 PD did not respond by the criterion of 50% reduction of the presenting deviation. However, an improvement of 10 PD in at least one of the components of deviation occurred in 2 of 4 patients with a deviation of 25 PD or more at presentation (patients 11 and 12, Table 2).

Fourteen of 15 myasthenic patients showed positive results for at least one of the ocular manifestations of myasthenia, diplopia or blepharoptosis, bringing the overall sensitivity of the test for the detection of myasthenia gravis to 93.33% (95% CI, 68.05%–99.83%) if diplopia response is evaluated by the lower threshold criterion.

Ptosis in the context of oculomotor nerve palsy either remained unchanged or even worsened by 1 to 1.5 mm in 2 patients with third-nerve palsy of microvascular origin. None of these patients had an improvement in their diplopia, either.

The ice test invariably showed negative results in all 4 patients with Horner's syndrome. Three of 4 patients with chronic progressive external ophthalmoplegia reported a subjective improvement that was measurable in terms of 1 to 1.5 mm of elevation of the eyelids and a mild improvement in ocular deviation not exceeding 30% reduction of the amount of ocular deviation (none of 4 tested patients had deviations exceeding 20 PD) in primary position.

Increasing the duration of cooling to 10 minutes also was investigated in 14 patients with oculomotor nerve paresis and in 13 patients with various strabismic entities (3 patients with fourth-nerve paresis and 4 patients with sixth-nerve paresis, 1 patient with hypertropia after cataract surgery, 1 patient with a history of orbital myositis, and 4 patients with chronic progressive external ophthalmoplegia). None of these patients responded to the 10-minute test.

## Discussion

After physiologic studies demonstrating a temperature-sensitive effect on repetitive nerve stimulation from myasthenic patients with local cooling,<sup>11,12</sup> Saavedra et al<sup>6</sup> sug-

gested a cold test that favorably influences neuromuscular transmission for the diagnosis of ocular myasthenia.

Subsequent studies<sup>4,8,13-15</sup> confirmed the diagnostic validity of the test in the evaluation of myasthenic ptosis and suggested 2 minutes as the optimum time of application of the ice pack, from the 5 to 10 minutes suggested initially.<sup>6,16</sup> The suggested threshold for a positive response in the evaluation of blepharoptosis is an elevation of the ptotic eyelid by 2.00 mm or more.<sup>4,8,14</sup>

The diagnostic value and the diagnostic criteria of the ice pack test for the assessment of myasthenic diplopia are not well defined, however, and despite its practicality, the test was reported by Thanvi and Lo<sup>10</sup> as "rarely performed in the UK." In the single reported series focusing on extraocular muscle responses, 15 of 15 myasthenic patients responded to orbital cooling "by dramatic improvement in alignment (no strabismus in primary position) or restoration of normal ductions."<sup>5</sup> No long-term follow-up was reported in the control group, and the authors acknowledge that some of these patients might have been myasthenic.

The authors' experience with the use of the ice pack has been quite different from the above. A partial rather than a complete resolution of diplopia was the rule for our patients. A decrease by half in at least one of the components of deviation in primary position was adopted as the threshold offering the optimum diagnostic value (sensitivity, 61.5%, and specificity, 98.2%, for the 5-minute application). Raising the threshold for a positive result to complete resolution of diplopia in primary position would have lowered sensitivity to 25% without increasing specificity. Had the threshold for improvement been lowered to 25%, sensitivity would have increased to 76.9% on initial application, but specificity would have decreased to 93.3% (95% CI, 83.61%–97.84%) because of 3 patients with chronic progressive external ophthalmoplegia responding to the test by this criterion.

The quantitatively small but consistent improvement in ptosis and extraocular muscle motility noted in the patients with chronic progressive external ophthalmoplegia has not been mentioned in the literature so far. It may denote a mild, nonspecific, facilitatory impact on muscle contractility in myopathic strabismus in general.

In patients with profound myasthenic impairment of ocular motility, the response to the ice pack tended to be less impressive. The authors suggest interpreting a decrease by 10 PD in the angle of strabismus after the ice pack test is applied for 5 minutes as diagnostic when the presenting deviation is larger than 20 PD. By incorporating this criterion, referred to as the *lower threshold* criterion, the sensitivity of the test reached 76.9% (95% CI, 49.06%–92.50%) without adversely affecting specificity.

Increasing the time of application to 10 minutes did not significantly improve sensitivity. The single patient who did respond to the 10-minute but not to the 5-minute application (patient 12, Table 2) would be considered a respondent anyway if the lower threshold for larger deviations were adopted.

The sensitivity for the assessment of myasthenic ptosis was superior to that for diplopia (92.3% vs. 76.9%,

Table 2. Results of the Ice Pack Test Application on Ptosis

Patient No.	Diagnosis	Age (yrs)	Gender	Marginal Reflex Distance (mm)	
				Before Ice Test*	After Ice Test <sup>†</sup>
1	Generalized MG	70	F	0.50	+2.50
2	Generalized MG, SLE	55	F	—	
3	OMG	70	F	1.00	+3.00
4	OMG	27	M	0.50	+3.50
5	Generalized MG	74	M	1.00, 2.00	+4.00, +3.00
6	OMG	66	M	1.5	+2.50
7	Generalized MG	56	F	1.50	+3.00
8	OMG	76	M	5.00, -0.50	+0.50, +4.00
9	Generalized MG	70	M	1.5	+3.5
10	OMG	47	F	1.00	+2.50
11	OMG	24	M	1.50	+1.50
12	Generalized MG	74	F	1.5	+3.50
13	OMG (Graves + IVth nerve palsy), thymoma	33	M	1.00, 4.00	+4.50, +2.00
14	Generalized MG, Graves, HIV+	52	M	Retraction	—
15	Generalized MG, Graves	79	M	6.00, -4.00	+1.50, +5.00

F = female; LHT = left hypertropia; LHPT = left hypotropia; LXT and LX(T) = left exotropia and left intermittent exotropia respectively; M = male; RHT = right hypertropia; SLE = systemic lupus erythematosus.

\*MRD measurements and alternate prism and cover test measurements (in prism diopters) immediately before the application of the ice pack.

<sup>†</sup>Difference in MRD measurements: MRD value immediately after removal of the ice pack minus MRD before the application of the ice test.

<sup>‡</sup>Alternate prism and cover test measurements immediately after the application of the ice pack for 5 minutes and 10 minutes, respectively.

<sup>§</sup>(+) or (—) indicates positivity for acetylcholine receptor antibodies. MUSK positivity is specifically indicated.

5-minute application, lower threshold criterion), but not to a statistically significant degree ( $P = 0.593$ , Fisher exact test).

The blepharoptosis response was positive in all but 1 patient who tested positively for diplopia. This latter patient's ophthalmoplegia (patient 11, Table 2) responded partially to the ice test and was considered positive only by the lower threshold criterion. Two myasthenic patients with a positive response for blepharoptosis had a false-negative result for diplopia (patients 8 and 15; Fig 1).

The specific value of the test in addressing diplopia of myasthenic origin is emphasized further by testing 3 patients (patients 13, 14, and 15, Table 2) with signs of concurrent dysthyroid ophthalmopathy, one of whom (patient 13, Table 2) also had evidence of congenital mild fourth-nerve paresis. The test proved consistent in selectively addressing the part of deviation attributable to myasthenia during recurrences in the latter case.

The high prevalence of myasthenia gravis among patients with dysthyroid ophthalmopathy (reportedly 0.2% in the literature) presents an extra challenge to the clinician who needs a reliable tool to orient the differential diagnosis in this not uncommon scenario. This is the reason why those 3 patients with the apparently confounding variable of dysthyroid ophthalmopathy were included in the final sensitivity ratio. Antimyasthenic treatment (including steroid administration in 2 of them) resulted in prompt resolution of symptoms in all 3 patients, confirming the predominantly myasthenic origin of diplopia.

False-positive results were noted in 3 patients in this series, 1 diagnosed with inflammatory fourth-nerve paresis and 2 patients with blepharoptosis: one had a history

of recurrent painful ophthalmoplegia and the other bearing the diagnosis of common pemphiga. There was an inflammatory-autoimmune common denominator in the etiopathogenesis of all 3 entities. No signs of external eye disease inflammation were documented in these patients. This association is noted, although a plausible explanation for a link between the peripheral site of action of the ice pack and the presumed inflammation-mediated etiopathogenesis of ptosis or diplopia in these 3 cases may not be offered. False-positive responses to the ice pack test have been reported very uncommonly in the literature.<sup>7</sup>

This study has to be viewed in light of its limitations. Variability in the presenting clinical picture is inherent to myasthenia and may pose methodologic problems in the interpretation of testing results and comparison of testing settings in the same patient. The authors thus believe that basing their conclusions on the initial evaluation is the best means to address the primary question in this study, that is, the value of this test as a preliminary test for myasthenia.

A major limiting factor in the interpretation of the results of this test is the standardization of the method of application of the ice pack. Bilateral simultaneous orbital cooling and the use of thin surgical gloves filled with ice cubes were adopted, as opposed to commercially available ice packs. The latter are associated with lower sensitivity, according to Ellis et al.<sup>5</sup> Special care was taken each time a surgical glove was filled with ice cubes so that the configuration of the ice pack allowed for the largest possible surface of apposition with the convex contour of the eyeball, thus maximizing the cooling effect on the extraocular muscles.

and Ophthalmoplegia in 15 Myasthenic Patients

Primary Deviation (MD)			Acetylcholine Receptor, Abs <sup>§</sup> , Muscle-Specific Kinase Results	Neostigmine Test Results
Before Ice Test*	5-Minute Ice Test <sup>‡</sup>	10-Minute Ice Test <sup>‡</sup>		
16 LHT, 6 LXT	6 LHT	6 LXT	+	
16 LHT	7 LHT	5 LHT	+	
10 RHpoT	5RHpoT	4 RHpT	+	+
4 HpoT	Ortho	Ortho		+
8 RET, 4 RHT	3 RET, 1 RH	2 RET	+++	
Ortho	Ortho	Ortho	-	+
11 RH	5 RH	5 RHT	+	
14 RET, 5 RHT	14 RET, 5 RHT	12 RET, 2 RHT	+	
10 LHpT	4 LHypT	2 LHypT	+	
—	—	—	-	+
35 LHT, 10 LXT	25 LHT, 8 XT	20 LHT	+	+
16 LHT, 8 LXT	7 LHT, 5 XT			
25 LHT, 10 LXT	14 LHT, 8 LXT	10 LHT, 8 LXT	+	
16 LHT, 15 LXT	6 LHT, 10 LXT		+	
22 LHT, 25 LXT	14 LHT, 14 LXT	12 LHT, 14 LXT		
20 LET, 3 LHT	7 LET, 3 LHT			
40 LX(T), 5 LHpT	35 LX(T), 5 LHpT	32 LX(T), 5 LHpT	MuSK+	
10 LX(T)	Ortho			
45 LXT, 10 LHpT	40 LXT, 6 LHpT	40 LXT	+	

MD = mean deviation; MG = myasthenia gravis; MRD = marginal reflex distance; OMG = ocular myasthenia gravis; RHpT = right hypotropia;

The need for customized care, however, may be considered suboptimal to standardization of testing conditions. Anatomic limitations in the exposure of extraocular muscles to the cooling effect of the ice pack may be responsible for lower sensitivity in the assessment of diplopia compared with blepharoptosis. With these anatomic restrictions in mind, the lower threshold criterion for larger angles of strabismus is suggested, although this is supported by evidence from a relatively small number of patients in this series.

Ensuring proper control of the head position is critical while cover test measurements are performed before and after the application of the ice pack test. Given the relatively small quantitative impact of the ice test in myasthenic deviation, one needs to eliminate gaze incomitance as a confounding factor in interpreting the results of the test. Immediate assessment of the ocular deviation after the ice pack is removed is critical because the effect of cooling is very short, in the order of 30 seconds to a few minutes. This is the reason the assessment was based on cover test measurements in primary position rather than on assessment of ocular motility.

Despite the availability of noninvasive tests such as lid fatigability in upgaze, the rest test, and the sleep test, establishing the diagnosis of myasthenia gravis necessitates the demonstration of positive AchR or MuSK antibodies, positive edrophonium or neostigmine test results, or a combination thereof.<sup>17</sup> Although highly specific for myasthenia, a false-negative rate of 40% to 50% has been reported for acetylcholine receptor antibodies.<sup>18,19</sup> The edrophonium

test long has been considered the gold standard for the diagnosis of myasthenia gravis with a sensitivity of 86% to 97% and a specificity of 83%.<sup>20,21</sup> However, it is time consuming with rare, but potentially serious, side effects, requiring careful monitoring of pulse and blood pressure. False-positive or paradoxical responses, like worsening of ocular alignment with edrophonium at a rate of 25%, have been reported.<sup>22,23</sup>

Major advantages of the ice test include its accessibility as a quick, noninvasive, inexpensive, safe, simple<sup>24</sup> preliminary test for orienting the diagnosis to myasthenia in the office. However, the physician should bear in mind that a partial rather than a complete response of ophthalmoparesis to the application of the ice pack may be expected. The threshold for a positive response offering the best diagnostic value in this series was a decrease by half in the angle of strabismus in primary position with the application of the test for 5 minutes. For angles of 25 PD or more, a decrease in the deviation by 10 PD could be considered diagnostic as well. By adopting this lower threshold criterion, the cumulative sensitivity of the test for assessing either manifestation of myasthenia gravis, ophthalmoparesis or blepharoptosis, was high (93.3%) in this series. However, the ice pack test proved of outstanding value in addressing diplopia of specifically myasthenic origin. A positive response when evaluating strabismus is highly suggestive of myasthenia even if multiple causes of diplopia coexist in the same patient. Potentially life-threatening causes of diplopia, ptosis, or both, such as oculomotor nerve palsy and Horner

**Figure 1.** Photographs of patient 15 (Table 2) showing coexisting myasthenia gravis and dysthyroid ophthalmopathy. Photographs showing (A) profound left blepharoptosis and ophthalmoplegia, which improved after (B) the application of the ice pack for 5 minutes. Photographs showing the same patient after the institution of antimuscarinic treatment (C) before and (D) after the application of the ice pack. Note bilateral eyelid retraction (D) resulting from concomitant thyroid eye disease, unraveled by the application of the ice pack.

syndrome, invariably were nonresponsive or even aggravated by the ice pack.

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## Footnotes and Financial Disclosures

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