



## Original Research Article

## Office investigations for myasthenia gravis: comparative analysis

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## ABSTRACT

**Introduction:** The purpose was to study the diagnostic yield of the various tests including lid fatigue test, Cogan twitch, Rest test, Ice test and Repetitive nerve stimulation (RNS) study in clinically diagnosed myasthenic patients.

**Materials and Methods:** A prospective study of newly diagnosed myasthenic patients was done at tertiary eye - care centre. Totally, 58 patients underwent tests for the confirmation of myasthenia gravis. Fishers Exact test was used for comparative analysis.

**Results:** Average age of presentation was 44.13 years. Number of male and female were 33 (56.9%) and 25 (43.1%). 8 (13.8%) patients were under the age of 15 years. Variability was observed in 47/58 (81.04%) patients and Fatigue was seen in 40 /58(68.97%) patients. Cogan twitch was observed in 28/58(48.28%) patients. Sensitivity of Rest test was 50%. Sensitivity of Ice test was 72.4%. Ice test positivity was 90% (9/10) in mild, 75% (21/28) in moderate, 68.75% (11/16) in severe ptosis indicating that increasing severity decreases the sensitivity. Sensitivity of combined Rest test and ice test was 90 %. Sensitivity of RNS study was 90%. The difference between the RNS study and Ice test was not statistically significant (p- 0.583). However RNS study showed higher percentage of positivity.

**Conclusion:** Ice test is more sensitive than rest test. Rest test and Ice test are simple, cost benefit bed side tests when combined, have sensitivity equivalent to RNS study. However RNS study is the gold standard confirmatory test.

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## 1. Introduction

The diagnosis of Myasthenia gravis made clinically in association with serological assays, pharmacologic tests and electrophysiological tests. Office investigations viz; Ice test, Rest test, Cogan twitch have been major contributory for the clinical diagnosis. Golnik et al in their study had the sensitivity of 80% for the ice test.<sup>1</sup> Singman et al stated that cogan lid twitch had sensitivity of 75% and specificity of 99%.<sup>2</sup> However there are no much studies in India to validate these tests in our population. Hence a prospective study was conducted to analyze these tests.

## 2. Materials and Methods

A prospective and analytical study was conducted in the Neuroophthalmology department of a tertiary eye care centre from 1st January 2012 and 31st August 2012.

All newly detected myasthenic patients of all age groups were included in the study. Patients whose results may be biased are excluded viz; Those who are already on treatment for MG, patients with restrictive myopathies, patients with orbital disease and /or inflammatory disease, patients with aponeurotic ptosis, patients who have undergone extra ocular surgeries previously, pregnant women/lactating women, patients with drug induced myasthenia and patients not willing to give consent were excluded.

MG was defined as isolated ptosis/diplopia at initial presentation supported by at least one of the following abnormal tests: Ice test, cogan lid twitch, lid fatigue test

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or greater than 10% decrement on repetitive stimulation.<sup>3</sup>

Demographic features, chief complaints like drooping of eye lids, double vision, and diurnal variation, previous thyroid disease and its treatment; Other systemic illness, treatment history including previous surgery were noted in the history. The visual acuity was measured using Snellen's Visual Acuity chart. Anterior segment and posterior segment evaluated in detail. After approval of the ethical committee, written informed consent was taken from all patients before enrolling in the study.

A clinical examination was performed and ptosis was graded with 15cm plastic ruler and hand held torch enabling patient's fixation as mild (up to 2 mm), moderate (3mm) and severe (4mm or more).

Suspected cases of ocular myasthenia gravis were subjected to relevant clinical test viz. eliciting Cogan's lid twitch sign, Rest test, lid fatigue test, Ice test. Fatigability was checked by asking the patient to look upward for 2 minutes, drooping of lids is noted.<sup>4</sup> Cogan twitch was checked by asking the patient to look down for 10 to 20 seconds and the patient is then asked to look in primary position, the upper eyelid twitching was noted.<sup>5</sup> Forrest test after complete ocular examination, each patient was taken to a quiet, darkened room and instructed to close the eyes.<sup>6</sup> 5 minutes later, the patient was asked to open the eyes and immediately the patient's palpebral fissures, ocular alignment, and ocular motility were measured. Ice test was performed as follows.<sup>5</sup> The size of the palpebral fissure was measured. A surgical glove containing crushed ice or ice cubes was then applied to the more involved eyelid for 2 minutes, with the opposite lid serving as a control. After 2 minutes, the glove was removed, and the size of the palpebral fissure was immediately measured. The test was considered positive if the size of the palpebral fissure is greater after cooling. Hess charting and diplopia charting were done wherever applicable to elicit range of limited extra ocular motility and direction of gaze with maximum separation of images (horizontal & vertical). Repetitive nerve stimulation study and CT thorax was done. All the patients were started on pyridostigmine with consultation of neurologist.

### 3. Results and Observation

In total, 58 patients were included. Patients were distributed in all age groups. Mean age of onset found to be 44.13 years (range 2-81 years). There were 33/58 males (56.9%) & 25/58 females (43.1%), showing slight male preponderance. Male to female ratio was 1.32:1.

Peak occurrence was observed in the 5th decade in both genders. 8(13.8%) patients were under the age of 15 years. Features were bilateral in 33 (56.9%) patients and unilateral in 25 (43.1%) of our patients. 34 patients (58.62%) had ptosis alone, 4 (6.9%) had EOM impairment alone and 20(34.48%) patients had both features. Majority of our

patients i.e. 54/58 (93.1%) had ptosis. The results of all the office investigations along with grading of ptosis are shown in Table 1.

Out of 116 eyes of 58 patients with myasthenia 31(26.72%) eyes had no ptosis, 17(14.65%) eyes had mild ptosis, 46 (39.65%) eyes had moderate ptosis, and 22 (18.96%) eyes had severe ptosis. Variability was observed in 47/58(81.04%) patients and Fatigue was seen in 40/58 (68.97%) patients. Cogan twitch was observed in 28 /58 (48.28%) patients.

EOM impairment was unilateral in 11 patients and bilateral in 13 patients. It was observed that 24 patients (41.38%) had motility impairment and 34 patients (58.62%) had normal motility. Orbicularis oculi weakness was noted in few i.e. 5/58(8.62%) patients. Rest test was positive in 29/58 patients. 0%. Rest test 0% (4/10) 28) in moderate ptosis, 43.75% (7/16) in severe ptosis. Ice test was 58 patients. Sensitivity of Ice test was 72.4%. Ice test positivity is 90 (9/10) in mild ptosis, 75% (21/28) in moderate ptosis, 68.75% (11/16) in severe ptosis.

Among the 58 newly detected myasthenic patients, 3 (5.17%) patients had previous history of thyroid disorder.

Out of 58 patients 38(65.57%) had no other systemic associations. Diabetes mellitus was found in 11/58(18.96%) patients. Hypertension was found in 10/58(17.24%) patients. Cardiac disease was found in 2/58(5.26%) patients. Insomnia was found in 2/58(5.26%) patients. Asthma was found in 1/58 (2.63%) patients. Chicken pox was found in 1/58(2.63%) patients. Among 58 patients 3 patients had of POAG, 1 patient had of myopia, and 2 patients had uveitis.

Out of 50 patients who have undergone RNS study, 45 (90%) patients showed positive response, 2 (4%) patients inconclusive response and 3(6%) patients showed negative response.

After excluding the patients, who are not giving consent for RNS study, the comparison between RNS study and Ice test was done. The difference between the RNS study and Ice test was not statistically significant (p- 0.583). However RNS study showed higher percentage of positivity. All the 15 patients who showed negative Ice pack test, showed decremental response with RNS study. And also 5 patients who did not show decremental response, showed positive ice pack test. Fisher exact test was used for comparative analysis.

### 4. Discussion

Myasthenia gravis (MG) is an autoimmune disorder of the neuromuscular junction, characterized clinically by variable muscle weakness and fatigability, caused by a reduction in the number of available ACh receptors at NMJs. The most commonly affected muscles are the levator palpebrae superioris, extraocular muscles.

**Table 1:** Showing the results of all the office investigations along with grading of ptosis.

S. No	Age	Sex	Ptosis (RE)	Ptosis (LE)	Fatigue	Cogan	Rest test	Ice test	RNS
1	60	F	Severe	moderate	p	N	N	P	P
2	22	M	no	moderate	p	P	N	P	P
3	64	M	moderate	moderate	p	N	P	P	P
4	36	F	mild	mild	N	P	N	P	P
5	35	F	moderate	moderate	p	N	P	P	P
6	33	F	moderate	severe	p	P	P	P	P
7	45	M	moderate	no	N	N	P	P	P
8	52	F	mild	no	p	N	N	P	P
9	26	F	mild	mild	p	N	P	P	P
10	31	M	no	mild	N	N	P	P	P
11	58	F	mild	mild	p	N	N	N	P
12	36	M	moderate	no	p	N	P	P	P
13	55	F	mild	no	N	P	P	P	P
14	57	F	moderate	no	p	N	N	N	P
15	60	M	severe	moderate	p	N	N	N	P
16	55	F	moderate	moderate	p	N	N	P	P
17	62	F	moderate	mild	p	N	P	P	N
18	53	M	no	no	N	P	P	P	P
19	9	M	no	severe	N	P	N	P	P
20	13	F	no	moderate	p	P	P	P	P
21	81	M	mild	mild	N	P	N	P	P
22	35	M	no	moderate	N	N	P	P	P
23	66	M	moderate	severe	p	P	P	P	P
24	11	F	no	severe	N	P	P	P	P
25	56	M	no	no	N	N	N	N	P
26	31	F	severe	no	p	P	N	P	N
27	42	F	moderate	no	p	P	N	P	P
28	51	M	no	moderate	p	N	P	P	P
29	5	M	mild	no	N	N	N	P	INC
30	70	M	moderate	mild	p	P	P	P	P
31	52	F	moderate	moderate	N	P	N	N	P
32	62	M	moderate	moderate	N	N	P	P	NA
33	70	F	no	moderate	p	P	N	N	P
34	45	M	mild	severe	p	N	N	P	P
35	33	M	severe	severe	p	N	P	P	P
36	47	M	moderate	moderate	p	N	N	N	P
37	8	F	moderate	no	N	N	N	P	P
38	52	M	no	severe	p	N	N	P	N
39	21	M	no	moderate	p	P	N	N	P
40	47	M	no	no	N	N	P	N	P
41	53	M	severe	severe	p	P	P	N	P
42	47	F	moderate	moderate	p	P	P	P	P
43	72	M	severe	severe	p	N	P	N	NA
44	50	M	mild	no	p	P	N	P	NA
45	65	M	no	mild	p	N	P	P	P
46	46	M	no	no	N	N	N	N	P
47	57	M	moderate	moderate	p	P	P	P	NA
48	63	M	no	moderate	N	N	P	P	P
49	19	M	severe	severe	N	N	N	N	P
50	2	M	moderate	moderate	p	P	P	P	INC
51	66	F	severe	no	p	P	N	N	P
52	10	F	moderate	moderate	p	P	N	N	P
53	62	F	moderate	moderate	p	P	P	P	P
54	12	M	severe	severe	p	N	P	P	NA
55	49	F	moderate	moderate	p	P	N	N	P
56	56	M	severe	severe	p	P	N	P	P
57	26	F	moderate	moderate	p	P	P	P	P
58	58	F	moderate	moderate	p	P	N	P	P

P=positive  
 N=negative  
 NA =not available

**Table 2:** Comparison of demographic data in various studies

	<b>Our study</b>	<b>B.S. Singhal<sup>7</sup> (Neurology, India)</b>	<b>Supinda<sup>8</sup> (Thai study)</b>	<b>Hyun Seok Roh<sup>9</sup> et al (Korean study)</b>
Study design	Prospective	Retrospective	Retrospective	Retrospective
Total no patients	58	841	90	71
Males	33[56.9%]	611[73.09%]	37[38.5%]	28[38%]
Females	25[43.1%]	225[26.91%]	59[61.5%]	43[62%]
Mean age of onset	44.13	48	37.3	41.8
In males	45.03	53	33.8	40.1
In females	42.96	34	39.5	42.8
Male:female	1.32:1	2.7:1	1:1.6	1.56:1
Thyroid positivity	5.17%		13.7%	7%

**Table 3:** Showing initial clinical presentation in various studies

<b>Initial clinical present</b>	<b>Our study</b>	<b>Kupersmith (New york)</b>	<b>Supinda<sup>8</sup> (Thai)</b>	<b>Hyun Seok Roh<sup>9</sup> et al (Korea)</b>
ptosis alone	58.62%	<1%	46.9%	1.5%
Diplopia alone	6.9%	<3%	13.5%	15.3%
Both	34.48%	64.%	39.6%	77.6%

**Table 4:** NS sensitivity in various studies

<b>Ref no</b>	<b>Study</b>	<b>Sensitivity</b>	<b>Country</b>	<b>Year of publication</b>
13	OZDEMIR AND YOUNG	95%	Turkey*	1976
14	Oh S J	77%	Birmingham	1992
15	Somnier FE	74.48%	Denmark	1993
16	Kennett [anconeus muscle]	35.29%	UK	1993
17	Wing Lok AU	69.9%	Singapore	2003
18	Rubin[facial muscles]	57%	USA 1	2004
7	Singhal	76.52%	India 1	2008
19	Evoli	5%	Italy	2009
11	Hyun Seok et al	82%	Korea	2010
20	Witoonpanich	73.2%	Thailand	2011
3	Mittal	24%	USA 2	2011
21	Yang Z X [children]	38%	China	2011
	Our Study	9%	India 2	

In, total 58 newly diagnosed patients of myasthenia gravis were included. Patients were distributed in all age groups (range 2-81 years) with mean age of onset was 44 years.

In our study there were 33 males (56.9%) & 25 females (43.1%) with mean ages of 45 and 42.96, respectively. Male to female ratio was found to be 1.32:1 indicative of male preponderance. Similar results were found in a retrospective study in India by Singhal<sup>7</sup> et al showing male preponderance.<sup>7</sup> In contrast other studies [Table 2] found female preponderance. As socio culturally men have easier access to tertiary health care than women in India, it is possible that mild cases of myasthenia gravis may have gone unreported.

In our study, features were bilateral in 33 (56.9%) patients and unilateral in 25 (43.1%) of patients. Similar results were obtained in a study in pediatric population by Steve et al showing bilateral presentation to be much

commoner than unilateral presentation.<sup>10</sup>

It was observed that 34(58.62%) patients had ptosis alone, 4 (6.9%) had EOM impairment alone and 20(34.48%) patients had both involvements. Similar results were seen in a retrospective study conducted by Supinda et al which reported that ptosis in 46.9%, only diplopia in 13.5% and both ptosis and diplopia in 39.6% of patients.<sup>8</sup> As shown in Table 3 results slightly vary.

The Ice test has been proposed as a relative simple means of diagnosing ocular myasthenia gravis, as myasthenic weakness has been found to improve with lowering of skeletal muscle temperature.

Golnik<sup>1</sup> et al in their study has concluded that ice test is a simple, short specific and sensitive test for the diagnosis of myasthenic ptosis where in positive ice test result was found in 16/20 (80%) patients with MG. The sensitivity of the ice test in patients with complete ptosis decreases considerably.

Kubis et al concluded that rest test and ice test show improvement of ptosis in myasthenia and not in non myasthenic ptosis and also that improvement is more in ice test compared to rest test.<sup>6</sup>

In our study Rest test was positive in 29/58 patients (50%) patients. Ice test was positive in 42/58 patients (72.41%) 58 patients. Hence ice test can be used as simple bed side confirmative test. Ice test have the decreasing order of sensitivity as severity increases.

Cogan twitch was observed in 28 (48.28%) patients. In contrast Singman et al, studied 117 patients presenting to neuroophthalmology clinic and found 18 /24 myasthenic patients having a positive lid twitch and stated that sensitivity of 75% and specificity of 99%.<sup>2</sup>

Orbicularis oculi weakness was noted in 5 /58(8.62%) patients. Osher concluded that 3/ 25(12%) patients with myasthenia gravis had orbicularis weakness in their study.<sup>11</sup>

Thyroid association was seen in 3/58 [5.17%] patients. Thyroid abnormalities are known to occur in 13% of patients. Among other systemic conditions; Diabetes mellitus, Hypertension had higher association value. Among 58 patients 3 patients showed association of POAG, 1 patient association of myopia, 2 patients had uveitis.

Out of 50 patients who undergone RNS study, 45 patients (90%) showed positive response and 2 patients (4%) inconclusive response and 3 (6%) patients showed negative response. As we see in the Table 4 the results vary significantly depending upon the test settings used. Singhal et al showed that 391/511 patients (76.51%) showed a decremental response.<sup>7</sup>

The difference between the RNS study and Ice test was not statistically significant. However RNS study showed higher percentage of positivity. All the 15 patients who showed negative Ice pack test, showed decremental response with RNS study. And also 5 patients who did not show decremental response, showed positive ice pack test. Combined rest test and Ice test has the sensitivity of 90% equivalent to that of RNS study.

Due to the ease of doing ice pack test, it can be used as an initial diagnostic test. In doubtful cases, RNS study can be used for confirmation.

## 5. Conclusions

Myasthenia gravis was distributed in all the age groups with peak age of onset at 5th decade with male preponderance.

Ice test is more sensitive than rest test. Ice test have the decreasing order of sensitivity as severity increases. Rest test and Ice test are simple, clinical, diagnostic bed side tests when combined, have sensitivity equal to that of RNS study. However RNS study is the gold standard confirmatory test.

### 5.1. Strengths and limitations of the study

It is a prospective study done in a tertiary eye care centre. But serological and pharmacological evaluation was not

done. Because only newly detected myasthenia patients were included, differentiation of generalized and ocular myasthenia could not be done. As the study was done in neuro ophthalmology department, specificity of these tests couldn't be evaluated.

### 5.2. Future recommendations

In future studies Anti Acetyl choline receptor antibody assay should be considered, which is more sensitive and specific test. Long term follow up is needed to assess the rate of conversion to generalized myasthenia.

## 6. Conflict of Interest

None.

## 7. Source of Funding

None.

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