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Effectiveness of different tests in the diagnosis of Ocular Myasthenia gravis

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Abstract

Background: Myasthenia gravis (MG) is an autoimmune neuromuscular disease leading to fluctuating muscle weakness and fatigue.Diagnostic tests include serum acetylcholine receptor antibody levels, Single fiber electromyography (SFEMG), Repetitive Nerve Stimulation (RNS) test, Neostigmin test, the sleep test, the rest test and the Ice pack test.

Objectives: To evaluate the importance and effectiveness of Ice pack test, Neostigmin test and RNS (Repetitive nerve stimulation test) in diagnosis of Myasthenia Gravis.

Materials and Methods: A hospital based prospective observational study was done in the Neuro-ophthalmology department in National Institute of Ophthalmology & Hospital, Dhaka (January 2014 to December 2014) among 30 patients who came with complaints of variable amount of ptosis and diplopia attending the neuro-ophthalmology department of NIO&H and who provided written informed consent were enrolled in the study. Those who came with any other ocular pathology or history of previous ocular surgery were not included in this study. The variable includes in this study were Gender, Age, Amount of ptosis, LPS function, Margin reflex distance, Ocular motility tests. We have performed the Ice pack test, then with proper arrangements Neostigmine test have been done in operation theater having emergency resuscitation and finally we refer all those patients to NINS&H (National Institute of Neuroscience & Hospital) for doing RNS (Repetitive nerve stimulation test), as our hospital does not have the facility for doing RNS test.

Results: Mean age was 31.72±6.46 years. Male preponderance was seen (56.67% of the cases). Most of the patients among them were within the age group of 11-20 years of age (40%).Ice pack tests was positive for 28 patients (93.33%) among 30 patients. Neostigmin test was also positive for 27 patients (90%) among of 30 patients. RNS test was positive only for 9 patients (32.1%).RNS test could not performed by 2 patients who were 5 & 6 years old respectively.

Conclusion: Most cases of clinically diagnosed Myasthenia gravis was positive by Ice pack tests (sensitivity 93.33%) and Neostigmin test (Sensitivity 90%). But RNS test was positive only those have systemic involvement or general Myasthenia Gravis (sensitivity 31.2%).So it is not so effective test for diagnosis of ocular myasthenia gravis.

Key words: Ptosis, Diplopia, Myasthenia Gravis, Ice pack test, Neostigmin test, RNS (Repetitive nerve stimulation test).

Introduction:

Myasthenia gravis (MG) is an autoimmune neuromuscular disease leading to fluctuating muscle weakness and fatigue. It is an autoimmune disorder, in which weakness is caused by circulating antibodies that block acetylcholine receptors at the postsynaptic neuromuscular junction.[1] inhibiting the excitatory effects of the neurotransmitter acetylcholine on nicotinic receptors throughout neuromuscular junctions.Ptosis, however, may be caused by a variety of disorders, so the distinction between myasthenic and nonmyasthenic ptosis is critical.[2] Myasthenia Gravis should be considered in every patient with ptosis and/ or diplopia.[3]

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Patients in between the age group (15-50) years are affected by MG. Female are more affected than male in younger patients. But alternatively in elder patients male are more affected.[4]

Diagnostic tests include serum acetylcholine receptor antibody levels, Single fibre electromyography (SFEMG), Repetitive Nerve Stimulation (RNS) test, Neostigmin test, the sleep test, the rest test and the Ice pack test.

A quick bedside technique for diagnosing Myasthenia Gravis is the Ice Test. [2, 5] Ice pack test is a simple diagnostic test that can be done in the clinic as an outpatient department procedure. It is highly sensitive and specific for Myasthenia Gravis. An ice pack is applied to the affected upper eyelid for 2 minutes. A positive test is the improvement of ptosis by > 2mm or more. The improvement of Myasthenia gravis with cooling probably occurs by lesser acetyl cholinesterase activity in temperature below 28^0C, providing increasing amount of acetylcholine molecules in the synaptic cleft. [6]

This prospective observational study have done among 30 patients with for the period of one year (from January, 2014 to December 2014) in the department of Neuro-ophthalmology ,National Institute of Ophthalmology and Hospital, NIO&H. It also includes demographic data of patients. With all ethical clearance, data have been collected with a preformed questionnaire. Data have been checked, cleaned and edited properly before analysis. Statistical analysis has been carried out by using v16.0 Windows statistical software. Descriptive statistics is used for the interpretation of the findings. There are few studies in world literature has been done on this subject.

Materials & Methods:

A hospital based prospective observational study was done in the Neuro-ophthalmology department in National Institute of Ophthalmology & Hospital, Dhaka (January 2014 to December 2014) among 30 patients who came with complaints of variable amount of ptosis and diplopia attending the neuro-ophthalmology department of NIO&H and who provided written informed consent were enrolled in the study. Those who came with any other ocular pathology or history of previous ocular surgery were not included in this study. The variable includes in this study were Gender, Age, Amount of ptosis, LPS function, Margin reflex distance, Ocular motility tests.

All patients with ptosis and diplopia underwent for complete history and proper evaluation, general, systemic and ocular examinations. Emphasis was given on visual acuity, amount of ptosis, LPS function, margin reflex distance, Fatigability test, Cogan lid twitch sign, Ocular motility test, Tonometry (IOP), cranial nerve examination require investigations, Complete blood count, ESR, Blood sugar, Serum creatinine, VDRL, Lipid profile, X ray chest (P/A view), ECG was also done.

Ice in between (0 to 4^0) centigrade is placed over the closed eyelids for 2 minutes. Before doing Ice pack test, MRD (margin reflex distance), LPS (Levator palpebrae superiosis) function. Palpebral fissure height (PFH) and amount of ptosis is measures and photograph is also taken for documentation. If ptosis improves by 2 mm or more, then Ice test is considered as 'Positive'.

Before doing Neostigmine test, all the patients were evaluated properly for systemic diseases and patients were sent to Anaesthesia department. NIO&H for general anaesthesia fitness. Counselling was done to all patients about the procedure, side effects and results.

After doing general anaesthesia fitness from anaesthesia department, a written informed consent is taken and patient is sent to operation theatre with resuscitation facilities for the examination procedure.

Weights of the patients were measured and I.V cannula was inserted for emergency resuscitation. Neostigmine methyl Sulphate (0.03 mg/kg body weight) and Atropine Sulphate (0.01 mg/kg body weight) was taken in 5cc disposable syringe. The medicine was injected in gluteal muscle (intramuscularly).

Before doing Neostigmine test, MRD (margin reflex distance), LPS (Levator palpebrae superiosis) function. palpebral fissure height (PFH) and amount of ptosis were measures and photograph was also taken for documentation. After injection, the aforesaid parameters were remeasured with 10 minutes interval for upto one hour with photographs (for documentation).

Improvement of ptosis 2 mm or more is considered 'Positive Neostigmine test'.

We referred all those patients to NINS&H (National Institute of Neuroscience & Hospital) for doing RNS (Repetitive nerve stimulation test), as NlO&H did not have the facility for doing RNS test at that time.

In RNS test, few muscles are usually examined, those are Trapezius, Biceps, Deltoid, EPB (Extensor pollicis brevis), Nasalis, Orbicularis oculi, ADM (Adductor digit minimi), APB (Abductor pollicis brevis). A train of 5 to 10 stimuli

is delivered at a rate of 2 to 3 Hz. A decrement greater than 10% is abnormal and suggesting neuromuscular junctional disorder like Myasthenia gravis.

Results

Thirty patients were enrolled in this study who came with the complaints of ptosis diplopia in the Neuro-ophthalmology department of National Institute of Ophthalmology & Hospital, Dhaka during the study period.

Table I: Characteristics of patients enrolled into the study at baseline

Characteristics	Frequency	Percentage (%)	p value
Gender[a]			
Male	17	56.67%	χ^2= 0.533
Female	13	43.33%	df=1
Total	30	100.0%	p = 0.465[ns]
Age group[a]			
01-10 years	04	13.33%	
11-20 years	12	40.00%	χ^2= 0.17.0
21-30 years	08	26.67%	df=5
31-40 years	01	3.33%	p =
41-50 years	02	6.67%	0.003*
51 and above	03	10.00%	
Mean age (Mean±SD)	24.03± 13.50 (5-55)		

[a]p value reached from Pearson's chi-square goodness-of-fit test,

*=significant, ns= Not significant

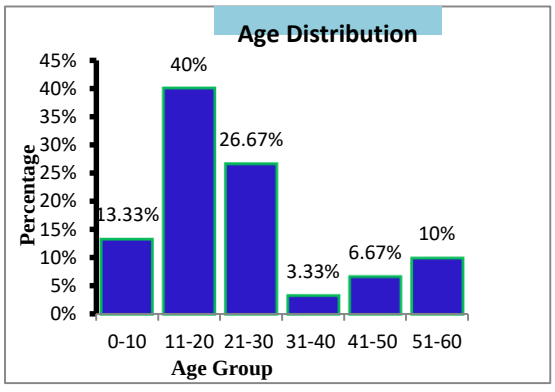

Figure I: Age distribution of the study subjects.

Figure shows those highest percentage age groups were in between (11-20) years 40% and lowest were (31-40) years 3.33%.

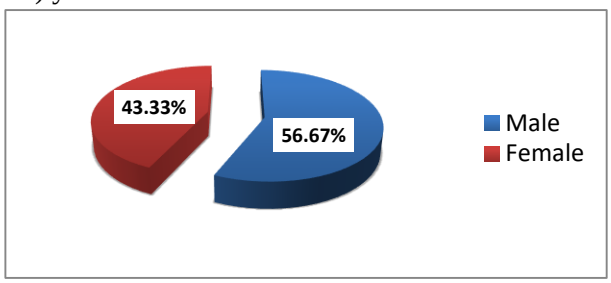

Figure II: Gender Distribution of study subject.

Figure shows that there were 17 male (56.67%) and 13 female (43.33%) were suffering from variable amount of ptosis and diplopia.

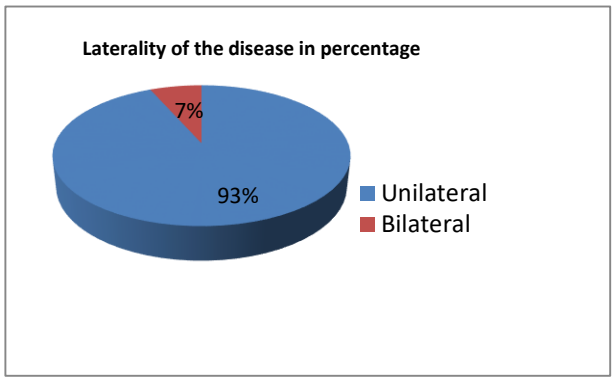

Figure III: shows the comparison of involvement of eyes in different patients.

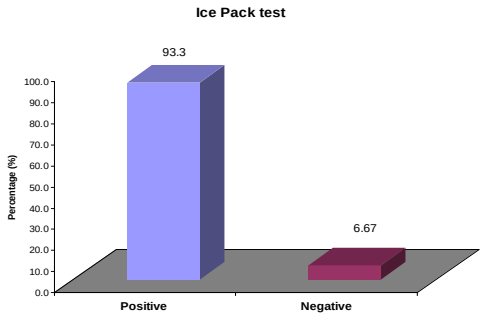

Figure IV: shows the comparison of positive and negative results of Ice test.

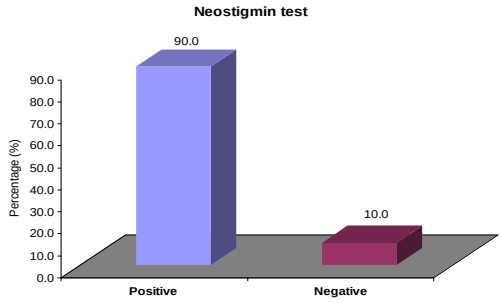

Figure V: shows the comparison of positive and negative results of Neostigmin test.

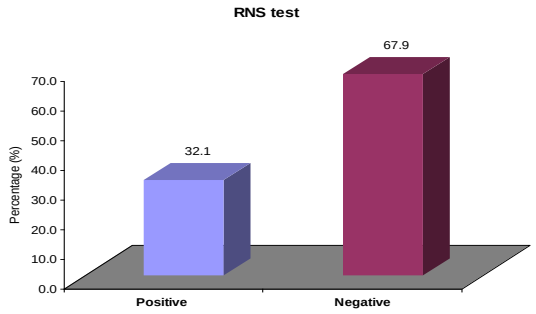

Figure VI: shows the comparison of positive and negative results of RNS test.

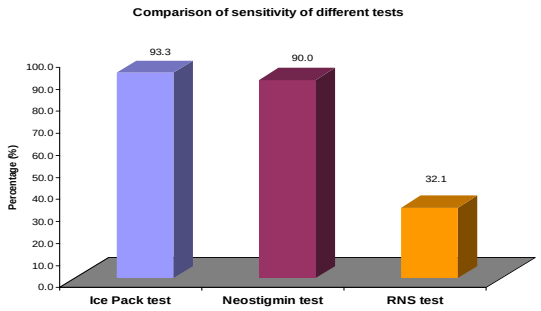

Figure VII: Comparison of sensitivity of different tests.

The figure shows that among 30 patients, Ice test was positive in 28 patients (93.33%), Neostigmin test was positive in 27 patients (90%), and RNS test was positive for 09 patients (32.10%).

Table II: Comparison of results of different tests.

No of patients	Positive		Negative		P value
	No.	%	No.	%	
Ice Pack test	28	93.33%	02	6.67%	χ^2= 22.53 df=1 p <0.001*
Neostigmin test	27	90.0%	03	10.0%	χ^2= 19.20 df=1 p <0.001*
RNS test	09	32.1%	19	67.9%	χ^2= 3.57 df=1 p =0.06^{ns}

p value reached from Pearson's chi-square goodness-of-fit test, *=significant, ns=non significant.

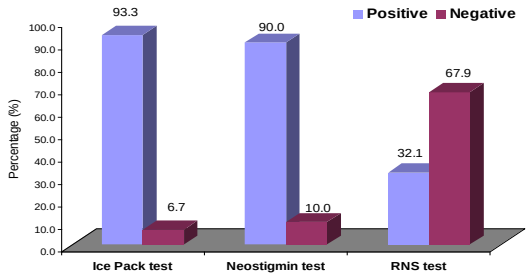

Figure VIII: shows comparison of different test with their positive and negative results

Discussion

Myasthenia gravis may have systemic manifestations, ophthalmic manifestations, or both. It may present with only ocular findings and then progress to generalized involvement. The differential diagnosis of ocular myasthenia includes ocular myopathy, muscular dystrophies, myotonic dystrophy, oculopharyngeal dystrophy, Lambert-Eaton myasthenic syndrome,botulism, Miller Fisher syndrome, intracranial lesions, mitochondrial myopathies including chronic progressive external ophthalmoplegia and Kearns-Sayre syndrome, thyroid eye diseases, drug-induced myasthenia, and traumatic and aponeurotic ptosis.[7]

Diagnostic tests for MG include the sleep test, the rest test, the Tensilon test, the acetylcholine receptor antibody assay, muscle biopsy, RNS (Repetitive nerve stimulation) test, SFEMG (Single fiber electromyography) and the Ice pack test. Simpson first described the effects of temperature in MG in 1960.[8] Bronestein and Desmedt showed that the local cooling improved myasthenic neuromuscular block, whereas warming had the opposite effect.[9] It is believed to affect the neuromuscular junction both by decreasing cholinesterase activity and by prompting efficacy of acetylcholine at eliciting depolarizations at the end plate. In our study we have shown that Ice test having some cooling effect, that means some change in temperature have some effect on improvement of ptosis in patients of MG. Ertaset al. in 1994 evaluated the ice test in 12 subjects with myasthenic ptosis and 15 control subjects. None of the control patients improved, whereas all patients (100%) with MG improved.[10]

Golink and coworkers confirmed previous findings regarding the ice test by showing improvement in ptosis of at least 2 mm in 16 of 20 patients with MG, with less than 0.5 mm of improvement in 20 control subjects, yielding a sensitivity of 80% and specificity of 100% if a positive test was defined as improvement of ptosis greater than or equal to 2 mm.[11]

Saavedra and coworkers in 1979 first described a cold test for MG used in evaluation of ptosis. They reported that myasthenic ptosis improved transiently in six patients after application of ice to the eye for 5 to 10 minutes. Two patients with nonmyasthenic ptosis did not improve.[12]

Sethi et al. in 1987 applied ice to a ptotic eyelid of 10 patients with MG and 7 without MG with the use of ice; 8 of the 10 subjects with MG had improvement in their ptosis. None of the subjects in the control group showed any improvement in their ptosis with the ice test.[13] In our study, it has been found that Ice pack kept over the closed ptotic eyelids for about 2 minutes and then evaluated and here among the 30 patients 28 patients have ptosis improvement after application of cold, non myasthenic ptosis did not improve. The result has similiarities with the previous study.

In our study the Ice test was positive for 28 patients among 30 patients. The sensitivity of the test was 93.33% and negative 6.67%. This result has similiarity with other studies [10-12] which have been done previously. Two patients were ice test negative, may be due to severe ptosis.

Tabassi et al**,** in 2005 showed that in their study, female were more affected by Myasthenia Gravis, 92 out of 156 patients (59%) and male 64 (41%) [14], whereas in our study we found an opposite scenario, male were more affected 17 out of 30 (56.67%) and female (43.33%) which was statistically insignificant (p=0.465). This difference may be due to female patients in our country deprived of proper treatment.

The mean age of the patients included in this study was 24.03 ± 13.50 years (range 05- 55 years) but in other study it was 29.32 years (range 3 to 75 years)[14].The highest incidence (40%) was in between age group (11-20)years.The result was statistically significant (p= 0.003).

The sensitivity of Ice test in our study was statistically significant (p< 0.001), which corresponds with other studies.[14]

In case of Neostigmin test, it was positive in 90% case and negative 10%. The result is statistically significant (p< 0.001), The result corresponds with other study where it is positive in 91% case.[15]

In Repetitive nerve stimulation test, it was positive only 32.1% case and negative (67.9%) for rest of the case. The result was statistically insignificant (p= 0.06).The result also corresponds with other study where RNS was positive 76% for generalized MG and 48% for ocular MG.[15] Most of the patients in our study had unilateral involvement of ptosis (93%), in comparison to bilateral involvement (07%).

Conclusion

Most cases of Myasthenia gravis was positive (sensitivity 93.33%) by Ice pack test. So, Ice pack test is a very sensitivity, non-invasive, cost effective, bed side test for the diagnosis of Myasthenia Gravis.Most cases of clinically diagnosed Myasthenia gravis was positive by Neostigmintests (Sensitivity 90%).But there are some difficulties in performing the test as life support facilities, cardiac and systemic evaluations etc. Bradycardia, nausea, vomiting, abdominal cramping are common side effects of this test.But RNS (Repetitive nerve stimulation test) test was positive only those have systemic involvement or general Myasthenia Gravis (sensitivity 31.2%).So it is not so effective test for diagnosis of ocular myasthenia gravis.

Limitation:

A limitation of our study was small populations (30 patients).

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Conflict of interest: None

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