Diagnostic accuracy and clinical utility of bed side tests versus laboratory tests in the diagnosis of ocular myasthenia

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Purpose: To assess the diagnostic accuracy of forced eyelid closure test (FECT), ice pack test (IPT), repetitive nerve stimulation test (RNS), and acetylcholine receptor (AchR) antibody test in patients with suspected ocular myasthenia. To assess the clinical utility of AchR antibody test in predicting disease progression. **Methods:** Retrospective cohort study of patients diagnosed with ocular myasthenia at a South-Indian neuro-ophthalmology tertiary eye clinic. Baseline characteristics; ocular myasthenia symptoms; results of FECT, IPT, RNS, and AchR antibody test; and progression time to generalized myasthenia (GM) over 36 months from the time of diagnosis were recorded and analyzed using receiver operator curve analysis, multiple logistic regression, and Kaplan–Meier survival analysis. **Results:** FECT had a sensitivity of 96.7% (95% CI: 88.5–99.6) and a specificity of 75% (95% CI: 34.9–96.8). Combination of FECT and IPT, using the positivity of at least one test, increased the sensitivity to 98.3% (95% CI: 91–100), reducing the specificity to 50% (95% CI: 15.7–84.3), whereas using the positivity of both tests, we obtained a sensitivity of 71.7% (95% CI: 58.6–82.5) and a specificity of 100% (95% CI: 63.1–100). In the subset of patients with double negative RNS and AchR antibodies, the positive predictive value of combined FECT and IPT (double positive) was 100%. Patients who developed GM were more likely to have a positive AchR antibody test result (*P* = 0.001). **Conclusion:** Combined FECT and IPT (double positive) has high diagnostic accuracy even among patients with normal RNS and negative AchR antibodies. Despite low sensitivity, AchR-antibody test has a significant predictive value in disease progression.

Key words: Acetylcholine receptor antibody, extra-ocular movements, forced eyelid closure test, ice pack test, myasthenia gravis, ptosis, repetitive nerve stimulation

Myasthenia gravis (MG) is an auto-immune disorder affecting the neuro-muscular junctions of skeletal muscles; 90% of MG patients present initially as ocular myasthenia.[1,2] There is no established gold standard test for the diagnosis of ocular myasthenia.[3] Ocular myasthenia can mimic cranial nerve palsy, inter-nuclear ophthalmoplegia, or thyroid eye disease.[4]

Edrophonium test is often used for confirmation and has a specificity of 97% but may be complicated by bradycardia and bronchiolar constriction,[5] Single-fiber electromyogram (SFEMG) is sensitive and specific for ocular myasthenia but is not widely available.[6] Acetylcholine receptor (AChR) antibody testing and repetitive nerve stimulation (RNS) tests are highly specific but less sensitive in ocular myasthenia (approximately 50%) compared with generalized MG (85%–90%).[7,8]

Our clinical experience suggests that easily available clinical bedside tests—forced eyelid closure test (FECT) and ice pack test (IPT)—have more diagnostic accuracy in cases of ocular myasthenia compared to the laboratory tests, namely RNS and AChR antibodies. We also noted an association between AChR

antibody positivity and progression from ocular myasthenia to generalized disease. To test these hypotheses, we attempted the following:

1. Compare the diagnostic accuracy of clinical tests (FECT and IPT) and laboratory tests (RNS and AChR antibody test) in patients with suspected ocular myasthenia
2. Assess the clinical utility of AChR antibody test in predicting disease progression

Methods

A retrospective cohort design was used. This is a single-center study at a neuro-ophthalmology clinic in a tertiary eye hospital. Following approval by the institutional review board, medical records were searched to identify patients diagnosed with ocular myasthenia from January 2016 to July 2017. Follow up period was 36 months from the time of diagnosis till July 2020. All patients included in this study have given written informed consent to utilize their de-identified data for research purposes. Our study adhered to the tenets of the Declaration of Helsinki.

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Data abstracted for each patient included age, gender, ocular symptoms (ptosis and/or diplopia), duration of follow-up, and progression time to generalized MG (if this occurred).

All patients with suspected ocular myasthenia referred to neuro-ophthalmology clinic underwent the following clinical evaluation:
1. Best-corrected visual acuity
2. Anterior and posterior segment examination using torchlight, slit-lamp biomicroscope, and + 90D fundoscopy lens
3. 9 gaze extraocular movement assessment
4. Hess and diplopia chart
5. Complete neurological exam
6. Fatigability test: Fatigability phenomenon was tested using forced eyelid closure test (FECT). To perform FECT, the patient was asked to squeeze his or her eyelids shut for 5–10 s and then open quickly and fixate in the primary position. The excessive upwards overshoot of eyelids movement indicated a positive FECT.
7. Ice pack test: The ice pack was held in place against the eyelids for 2 min. The evaluation was performed by recording the upper MRD with a millimeter ruler, immediately before and after applying the ice pack. The test was considered positive if there was an improvement of more than 2 mm of MRD or symptomatic relief in diplopia.
8. Intraocular pressure using noncontact tonometer
9. Blood pressure- manual sphygmomanometer

Following a probable clinical diagnosis of ocular myasthenia based on the above tests, patients were referred for the following tests:
A) RNS: The facial nerve supplying orbicularis oculi was electrically stimulated 6–10 times at 3 or 5 Hz, and the compound muscle action potential (CMAP) was recorded with surface electrodes. Decremental response in CMAP greater than 10% was considered to be indicative of ocular myasthenia.
B) AchR antibodies - serum testing for the AChR binding antibody (muscle AChR complexed with 125I-labeled-α-bungarotoxin; Lister Laboratories and Diagnostics), with values > 0.02 nmol/L considered a positive result
C) CT chest to rule out thymoma

In addition, thyroid function test and blood glucose were also done. Neuro-imaging was not routinely done in all patients unless indicated. Single-fiber electromyogram (SFEMG) and MUSK antibody test were not done in our patients due to nonavailability of these tests.

The diagnosis of ocular myasthenia was made when at least one of the standard diagnostic tests for myasthenia gravis was positive in the absence of other causes. These included:
1. Presence of AChR antibodies
2. Decrement >10% of the third to fifth compound muscle action potential with respect to the first after RNS
3. Positive intramuscular neostigmine test (done when other tests are inconclusive)
4. Unequivocal response to oral steroid and/or acetylcholinesterase inhibitors for a period of at least 3 months

The results of FECT and IPT were not used for establishing the final diagnosis.

Patients received treatment under the combined care of a neurologist and a neuro-ophthalmologist. Following confirmation of diagnosis, patients were started on pyridostigmine, an acetylcholinesterase inhibitor (AChEI) as first-line therapy. Patients not responding to pyridostigmine were switched to low dose alternate days oral corticosteroids (prednisone 20 mg/day) with or without continued pyridostigmine. Patients who could not tolerate long-term steroids were initiated on immune suppressants including azathioprine or mycophenolate mofetil. All patients were followed up for a period of 36 months to monitor progression to generalized myasthenia. Of the 68 patients, 46 patients required steroids in addition to AChEI for adequate symptomatic relief.

Sample size
Given the absence of validated methods for a priori sample size estimate in the context of retrospective studies, we used past years' estimates of population size and population proportion to arrive at a sample size.

Population proportion: 4.4%

Population size: 2500

Sample size needed to have a CI of 95% and margin of error 5%: 63 or more.

Statistical analysis
Continuous variables are presented as mean ± standard deviation (SD), and categorical variables as absolute and relative frequency (%). Fisher's exact test was used to evaluate the univariate association between the results of test combination and other variables. Results are presented as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) with respective 95% confidence intervals (CI). ROC analyses were used to assess the diagnostic accuracy of FECT, IPT, and RNS. DeLong test was used to compare the area under the curve (AUC) of the different tests and their combination with the reference test. Bonferroni correction was applied when appropriate. Multiple logistic regression was used to measure the association between all measured clinical variables and antibody result. Progression to generalized MG was compared by age and sex as well as antibody status with Kaplan–Meier estimates and log-rank tests. Statistical analysis was performed using statistical package Stata SE, 14.2.

Results

Population
During the study period, 112 patients with suspected ocular myasthenia were referred from the general ophthalmology outpatient services to our neuro-ophthalmology clinic. Of these, 68 patients were included in the study. Following were excluded:
- Thirteen patients had other diagnoses (vasculopathic cranial nerve palsy: 5, chronic progressive external ophthalmoplegia: 1, Internuclear ophthalmoplegia: 3, cavernous sinus Tolossa Hunt syndrome: 1, thalamic lacunar infarct: 1, gaze palsy: 2).
- Nineteen patients did not complete the 36-months follow-up.
- Forced eyelid closure test was not documented in six patients.

- Nine patients had not undergone antibody testing.
- Three patients were in the pediatric age group. Patients less than 18 years were not included in the study.

Of the 68 patients included, 43 (63.2%) were males and 25 (36.8%) females. The mean (SD) age at the time of diagnosis was 48.96 years. Presenting symptoms included ptosis in 10 (14.7%), diplopia in 24 (35.3%), and ptosis and diplopia in 34 (50%) [Table 1].

Diagnostic yield of clinical and laboratory tests

The sensitivity, specificity, and positive predictive value of various tests are given in Table 2.

FECT was positive in 64 (94.1%) patients. IPT was positive in 49 (72.1%) patients. IPT's positivity was more frequent in patients with isolated ptosis compared to patients with diplopia and ptosis (97.3% vs. 83.6%, *P* = 0.04) and in those with severe ptosis compared to patients with moderate (100% vs. 84.2%, *P* = 0.002) or mild (100% vs. 58.8%, *P* < 0.0001) ptosis. Patients with isolated

Table 1: Patient characteristics

Characteristics	Values[a] (*n*=68)
Age in years	
Mean (SD)	48.41 (7.5)
Range	29-65
Sex	
Female	25 (36.76)
Male	43 (63.24)
Symptoms	
Ptosis only	10 (14.71)
Ophthalmoplegia	24 (35.29)
Ptosis & Ophthalmoplegia	34 (50.0)
AChR antibody result	
Positive	25 (36.76)
Negative	43 (63.24)
Progression to generalized myasthenia	
Yes	13 (19.12)
No	55 (80.88)

[a]Data are presented as percentage (frequency) of patients; *n* - number of participants. AchR=acetylcholine receptor
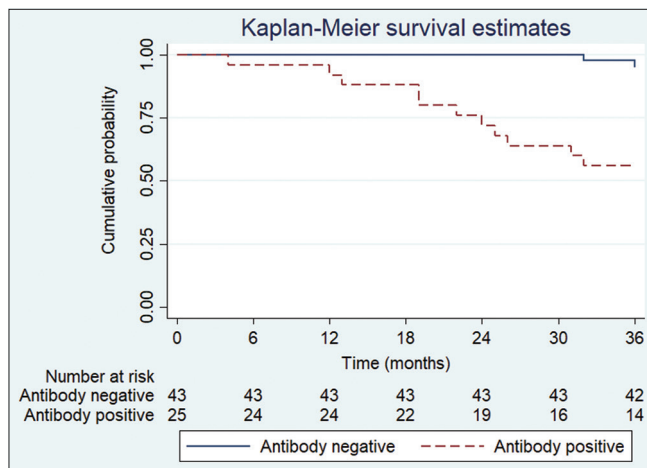
Figure 1: Proportion of patients by antibody status with ocular myasthenia that did not progress to generalized myasthenia (*n* = 68). Antibody status was significant by the log-rank test (*P* < 0.001)

diplopia showed no response to IPT. RNS showed decremental response in 44 (64.7%) patients. AChR antibody was positive in 25 (36.8%) patients. Sixty patients responded to the initial AChEI and the remaining eight responded to steroid therapy.

The majority of cases had at least one diagnostic criteria before receiving therapy; however, in up to 11.7% of cases, the diagnosis was based only on the response to steroid therapy and the absence of other identifiable causes.

FECT and IPT in patients with double-negative RNS and AChR-abs

As the FECT and IPT can be especially useful in those patients with suspected ocular myasthenia who have negative RNS and AChR-abs, we evaluated the accuracy of FECT, IPT, and combined FECT and IPT (at least one positive) in these patients [n = 15; Table 3]. In this population of double negative RNS and AChR antibody, the sensitivity and specificity of FECT was 100% (95% CI: 69.2–100) and 80% (95% CI: 28.4–99.5), respectively; Sensitivity and specificity of IPT was 70% (95% CI: 34.8–93.3) and 40% (95% CI: 5.3–85.3), respectively.

Specificity of combined FECT and IPT (at least one positive) was 20% (95% CI: 0.5–71.6); However, specificity of combined FECT and IPT (both positive) was 100% (95% CI: 63.1–100).

Utility of AChR antibody in ocular myasthenia

Acetylcholine receptor antibody test results were positive in 25 (36.8%) patients. Thirteen (19.1%) patients out of the 68 patients developed generalized MG, out of which AChR antibody was positive in 11 (16.2%) patients at the time of diagnosis. All patients included were followed up for 36 months.

Patients who developed generalized symptoms were more likely to have a positive AChR antibody test result (OR: 25.07; 95% CI: 4.08–154.06; *P* = 0.001). Presentation with diplopia, ptosis, or both did not significantly predict antibody status. Age at diagnosis [OR: 1.03, 95% CI: 0.95–1.12, *P* = 0.455), gender (OR: 0.37, 95% CI: 0.09–1.46, *P* = 0.155), and combined variable looking at the interaction of age and sex did not significantly predict positive antibody status [Table 4]. None of our patients included in our study had symptoms of generalized myasthenia at presentation. Kaplan–Meier curves for progression to generalized MG based on antibody status are illustrated in Fig. 1. The log-rank test was significant for antibody status (*P* = 0.001) but not for age (*P* = 0.455) or sex (*P* = 0.155).

Table 5 shows the distribution of patients according to FECT and treatment response. The presence of double positivity was significantly associated with the presence of AchR antibodies.

Discussion

Around 50%–85% of patients with ocular myasthenia progress to generalized myasthenia; 90% of these patients progress within 2 years of onset of the disease.[9,10] Currently available diagnostic tests, including RNS, SFEMG, and AChR-Abs, have higher diagnostic accuracy in cases of generalized myasthenia but show varying levels of sensitivity in ocular myasthenia.

In our clinical experience, we find the clinical bedside noninvasive tests, including forced eyelid closure test and ice pack test, to be of more diagnostic value in identifying ocular

Table 2: Accuracy of FECT, IPT, RNS, and AchR antibody test in patients with ocular myasthenia

Test type	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUROC Area (95% CI)
FECT	96.7% (88.5-99.6)	75.0% (34.9-96.8)	96.7% (88.5-99.6)	75.0% (34.9-96.8)	0.858 (0.696-1.0)
RNS	68.3% (55.0-79.7)	62.5% (24.5-91.5)	93.2% (81.3-98.6)	20.8% (7.1-42.2)	0.654 (0.465-0.843)
Ice Pack	73.3% (60.3-83.9)	62.5% (24.5-91.5)	93.6% (82.5-98.7)	23.8% (8.2-47.2)	0.679 (0.491-0.867)
AchR antibody	41.7% (29.1-55.1)	100% (63.1-100)	100% (86.3-100)	18.6% (8.4-33.4)	0.708 (0.645-0.771)
Single positive (FECT & RNS)[a]	98.3% (91.1-100)	50.0% (15.7-84.3)	93.7% (84.5-98.2)	80.0% (28.4-99.5)	0.742 (0.556-0.928)
Double positive (FECT & RNS)[b]	66.7% (53.3-78.3)	87.5% (47.3-99.7)	97.6% (87.1-99.9)	25.9% (11.1-46.3)	0.771 (0.634-0.907
Single positive (FECT & IPT)[a]	98.3% (91.1-100)	37.5% (8.5-75.5)	92.2% (82.7-97.4)	75.0% (19.4-99.4)	0.679 (0.499-0.859)
Double positive (FECT & IPT)[b]	71.7% (58.6-82.5)	100% (63.1-100)	100% (91.8-100)	32.0% (14.9-53.5)	0.858 (0.801-0.916)

PPV=positive predictive value; NPV=negative predictive value; AUROC=area under the receiver operating curve; CI=confidence interval; FECT=forced eyelid closure test; RNS=Repetitive nerve stimulation; AchR=acetylcholine receptor; IPT=ice pack test. [a]For single positive, we considered as an indicator of ocular myasthenia the positivity of at least one test. [b]For double positive, we considered as suggestive of OM the positivity of both tests.

Table 3: FECT and IPT in patients with double negative RNS and AchR antibodies

Test type (n=15)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUROC Area (95% CI)
FECT	100% (69.2-100)	80% (28.4-99.5)	90.9% (58.7-99.8)	100% (39.8-100)	0.9 (0.70-1.0)
Ice Pack	70% (34.8-93.3)	40% (5.3-85.3)	70% (34.8-93.3)	40% (5.3-85.3)	0.55 (0.27-0.83)
Combined (FECT + IPT)[a]	100% (69.2-100)	20% (0.5-71.6)	71.4% (41.9-91.6)	100% (2.5-100)	0.6 (0.40-0.80)
Combined (FECT + IPT)[b]	70.0% (34.8-93.3)	100% (47.8-100)	100% (59.0-100)	62.5% (24.5-91.5)	0.85 (0.7-1.0)

FECT - forced eyelid closure test; RNS - Repetitive nerve stimulation; AchR - acetylcholine receptor; IPT - ice pack test; PPV - positive predictive value; NPV - negative predictive value; AUROC=area under the receiver operating curve; 95% CI=95% confidence interval. [a]At least 1test (FECT or IPT) positive; [b]Both tests (FECT and IPT) positive

Table 4: Multiple logistic regression predicting acetylcholine antibody positivity

	AChR Antibody		Adjusted Odds ratio		
	Positive	negative	OR	95% CI	P
Age					
Mean (SD)	48.96 (7.5)	48.09 (7.5)	1.03	0.95-1.12	0.455
Gender					
Male*	17 (68.0)	26 (60.5)	0.37	0.09-1.46	0.155
Female	8 (32.0)	17 (39.5)			
Progression					
No*	14 (56.0)	41 (95.4)	25.07	4.08-154.06	0.001
Yes	11 (44.0)	2 (4.6)			
Ptosis			a	-	-
No*	25 (100)	33 (76.7)			
Yes	-	10 (23.3)			
Diplopia			0.69	0.27-3.6	0.67
No*	16 (64.0)	28 (62.1)			
Yes	9 (36.0)	15 (34.9)			
Ptosis with Diplopia			0.77	0.35	0.33
No*	9 (36.0)	25 (58.1)			
Yes	16 (64.0)	18 (41.9)			

AChR - Acetyl choline receptor, OR - Odds Ratio; CI - Confidence interval. *Reference category; a A cell frequency is empty for the ptosis and antibody comparison, hence regression could not be done

myasthenia. To test this hypothesis, we conducted this study. We also wanted to assess the clinical utility of AChR antibody testing in predicting disease progression.

Forced eyelid closure test (FECT) was first described by Don C. Bienfang, MD, a neuro-ophthalmologist at Harvard Medical School, in 1982. This is a lesser-known test compared to Cogan's lid twitch and ice pack test for clinical screening of ocular myasthenia.

Validity of FECT has been studied by Apinyawasisuk *et al.*[11] in 2018 and was proven to be a sensitive and specific tool in screening ocular myasthenia. In our study, we found that FECT has the highest diagnostic yield compared to

Table 5: Distribution of ocular myasthenia cases according to forced eyelid closure test and treatment response

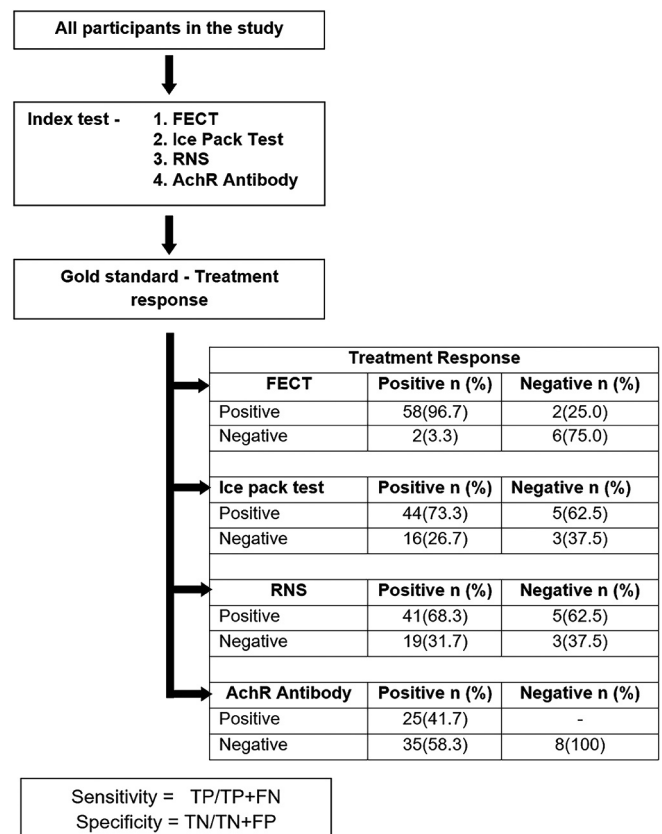|	FECT positive (%)	Treatment response[a] positive (%)	Both Positive (%)	Both Negative (%)	P
Number of patients (*n*=68)	2 (2.9)	2 (2.9)	58 (85.3)	6 (8.8)	
Age mean +/- SD	52.5 (6.4)	45.0 (9.9)	48.2 (7.7)	50.5 (3.4)	0.642[K]
Gender					>0.999[F]
Male	1 (50.0)	1 (50.0)	37 (63.8)	4 (66.7)	
Female	1 (50.0)	1 (50.0)	21 (36.2)	2 (33.3)	
Clinical Features					0.810[F]
Ptosis	-	-	8 (13.8)	2 (33.3)	
Diplopia	1 (50.0)	1 (50.0)	21 (36.2)	1 (16.7)	
Ptosis and Diplopia	1 (50.0)	1 (50.0)	29 (50.0)	3 (50.0)	
AChR-Ab test					0.015*[F]
Negative	2 (100)	-	35 (60.3)	6 (100)	
Positive	-	2 (100)	23 (39.7)	-	
Ice Pack Test					0.057[F]
Negative	2 (100)	1 (50.0)	15 (25.9)	3 (50.0)	
Positive	-	1 (50.0)	43 (74.1)	3 (50.0)	
RNS					0.235[F]
Negative	1 (50.0)	1 (50.0)	18 (31.0)	4 (66.7)	
Positive	1 (50.0)	1 (50.0)	40 (69.0)	2 (33.3)	

[a]Treatment response was defined as unequivocal response to oral steroid and/or acetylcholinesterase inhibitors for a period of at least 3 months. K - Kruskal Wallis test; F - Fisher's exact test; FECT - Forced eyelid closure test; AchR - Ab-acetylcholine receptor antibody; RNS - repetitive nerve stimulation; *Significant result

IPT, RNS, and AChR antibody test. Table 2 compares the sensitivity, specificity, and positive and negative predictive values of the clinical and laboratory tests used in this study. Treatment response was used as the reference standard to compare these tests [Fig. 2] as there is no established gold standard test for diagnosis of ocular myasthenia. Treatment response was defined as unequivocal response to oral steroid and/or acetyl cholinesterase inhibitors for a period of at least 3 months.

Sensitivity of FECT was 96.7% (95% CI: 88.5–99.6) with a specificity of 75% (95% CI: 34.9–96.8) and a positive predictive value of 96.7% (95% CI: 88.5–99.6). Combined FECT and IPT (at least one positive) had the highest sensitivity of 98.3% (95% CI: 91.1–100) with a positive predictive value of 92.2% (95% CI: 82.7–97.4). However, the sensitivity of combined FECT and IPT (both positive) was 71.7% (95% CI: 58.6–82.5). However, the specificity when both FECT and IPT were positive was 100% (95% CI: 63.1–100) with a positive predictive value of 100% (95% CI: 91.8–100).

False-negative rate of FECT was low in our study. Out of the 68 patients, four patients had false-negative FECT. At the time this false-negative FECT was performed, two patients had already received steroids from elsewhere for diplopia and one patient had dermatochalasis. False-positive FECT was noted in two patients whose final diagnoses were decompensated phoria and Lambert–Eaton myasthenia syndrome, respectively.

The sensitivity and the specificity of IPT in our cohort were 73.3% (95% CI: 60.3–83.9) and 62.5% (95% CI: 24.5–91.5), respectively. A study by Giannoccaro *et al.*[12] reported that IPT and SFEMG have a similar diagnostic accuracy in patients with ocular myasthenia presenting with ptosis. Though IPT is shown to be equally accurate to SFEMG, it can be demonstrated only in patients presenting with ptosis. IPT cannot be used to screen patients presenting with isolated diplopia.

Figure 2: Comparison of the sensitivity, specificity, and positive and negative predictive values of the clinical and laboratory tests used in this study. Treatment response was used as the reference standard to compare these tests. Treatment response was defined as unequivocal response to oral steroid and/or acetylcholinesterase inhibitors for a period of at least 3 months. FECT = forced eyelid closure test; RNS = repetitive nerve stimulation; AchR = acetylcholine receptor

Sensitivity of RNS was 68.3% (95% CI: 55.0–79.7) with a positive predictive value of 93.2% (95% CI: 81.3–98.6). No statistical significance was found between the ROC curve of FECT, IPT, and RNS compared to the reference standard (treatment response).

A subset of 15 patients in our study was double negative for RNS and AChR-Ab.

The FECT and IPT still showed good diagnostic accuracy in these patients with normal RNS and negative AChR antibodies. FECT was positive in all 15 patients in this subset. Sensitivity of IPT was 70% (95% CI: 34.8–93.3). The positive predictive value of combined FECT and IPT (double-positive) was 100% (95% CI: 59.0–100). The negative predictive value of combined FECT and IPT (at least one positive) was 100% (95% CI: 2.5–100), indicating that if both these tests are negative, the diagnosis of ocular myasthenia is highly unlikely. Therefore, either the negativity or the positivity of both tests significantly changed the post-test probability of the diagnosis even in patients with double negative RNS and AChR antibodies.

We would like to emphasize that FECT formerly known as Bienfang test is a simple, quick, noninvasive test and should be used as a valuable screening tool for ocular myasthenia. It is especially valuable in patients of suspected ocular myasthenia with normal RNS and negative antibodies. Its advantage over IPT is that it can also be demonstrated in patients without ptosis. It has a higher sensitivity compared to RNS and AChR-abs in cases of ocular myasthenia and is demonstrable even in early stages of the disease.

Previous estimates of the rate of antibody positivity in patients with ocular myasthenia vary from 40% to 70%.[13] Our result of 41% (95% CI: 29.1–55.1) sensitivity falls at the lower limit range. A possible explanation for our lower rate of AChR antibody sensitivity lies in the association between antibody levels and the duration of MG symptoms. Vincent and Newsom-Davis suggested that the high affinity of antibodies for end-plate AChRs at the neuromuscular junction could explain why some patients with OMG have negative serum test results early in the course of the disease but later seroconvert.[14] It is not until an individual reaches a certain level of receptor-binding saturation that antibodies begin to freely circulate in the peripheral blood. Because many of our patients were seen in the early stages of the disease, it is possible that they had lower levels of circulating antibodies for detection.

Although the sensitivity of AChR-Abs was found to be low in our study, a significant effect of antibody positivity on the risk of progression to generalized MG was evident in our cohort based on the Kaplan–Meier estimate [Fig. 1] and log-rank tests. Kupersmith et al.[15] and Peeler et al.[16] also reported a significant association between positive AChR antibody test results in ocular myasthenia and the risk of progression to generalized MG.

In our study of 68 patients, 13 progressed to generalized myasthenia within the follow-up period of 36 months. Among the 13 patients, progression was noted as early as month 4 since the time of initial diagnosis in only one patient. The remaining patients showed progression between months 12–36 from the time of initial diagnosis. Rate of progression in our cohort was 19% at the end of 3 years follow-up as opposed to the existing literature that states that 50%–80% of ocular myasthenia will progress to generalized myasthenia among which 90% will progress within 2 years. The reason for lower rate of progression might be because of early initiation of corticosteroids in our patients.

Currently, there is limited evidence favoring the use of immune modulators in treating ocular myasthenia. Various studies on the effect of prednisone on the progression of ocular to generalized myasthenia have stated that the early use of steroids decreases the progression in these patients.[4,17,18]

In our cohort of 68, 13 patients progressed to generalized myasthenia despite early AChEI/corticosteroid therapy. Out of these 13, 11 had AChR-Abs positivity at the time of diagnosis. We believe that this finding adds clinical value to antibody testing and will improve its utility as a prognostic tool. Although the sensitivity of antibody testing in ocular myasthenia is variable, it has a significant predictive value in disease progression, suggesting that patients with ocular myasthenia and positive AChR-abs require closer follow-up with consideration for early immunosuppressant therapy.

Conclusion

There are various limitations in our study. SF-EMG results could not be analyzed due to its nonavailability. The positivity and negativity of FECT were determined by a single neuro-ophthalmologist. Inter-observer reliability needs to be addressed in future studies. There is no generally accepted gold standard test for ocular myasthenia. Using an imperfect reference standard produces reference standard bias. To evaluate diagnostic tests with no existing reference standard, applying the concept of clinical test validation can provide a significant methodological advantage over the traditional test accuracy paradigm. In our study, we used treatment response as the reference standard to arrive at the diagnostic accuracy of FECT, IPT, RNS, and AChR-antibody test.

Conflicts of interest

There are no conflicts of interest.

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