Title
Validity of Forced Eyelid Closure Test

Journal
Journal of Neuro-Ophthalmology, 37(3)

ISSN
1070-8022

Authors
Apinyawasisuk, Supanut
Zhou, Xinkai
Tian, Jack J
et al.

Publication Date
2017-09-01

DOI
10.1097/wno.0000000000000514

Peer reviewed

Published in final edited form as:

J Neuroophthalmol. 2017 September ; 37(3): 253–257. doi:10.1097/WNO.0000000000000514.

Validity of forced eyelid closure test: a novel clinical screening test for ocular myasthenia gravis

Supanut Apinyawasisuk, MD[1,2,3], **Xinkai Zhou, MS**[4], **Jack J. Tian**[1,5], **Giancarlo A. Garcia, AB**[1,6], **Rustum Karanjia, MD, PhD**[1,7], and **Alfredo A. Sadun, MD, PhD**[1]

[1]Doheny Eye Center, Department of Ophthalmology, David Geffen School of Medicine, UCLA, Los Angeles, CA, USA [2]Ophthalmology Department, King Chulalongkorn Memorial Hospital, Bangkok, Thailand [3]Department of Ophthalmology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand [4]Department of Medicine, Statistics Core, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA [5]David Geffen School of Medicine, UCLA, Los Angeles, CA, USA [6]University of California-Irvine School of Medicine, Irvine, CA, USA [7]The Ottawa Eye Institute, University of Ottawa, Ottawa, ON, Canada

Abstract

Corresponding author: Supanut Apinyawasisuk, s.apinyawasisuk@gmail.com, 1873 Rama 4 Road, Pathumwan, Bangkok 10330, Thailand, Tel. +66817013300.

The authors report no conflict of interest.

Statement of Authorship
Category 1:
a. Conception and design
Supanut Apinyawasisuk
Xinkai Zhou
Rustum Karanjia
Alfredo A. Sadun
b. Acquisition of data
Supanut Apinyawasisuk
Jack J. Tian
Giancarlo A. Garcia
c. Analysis and interpretation of data
Xinkai Zhou
Alfredo A. Sadun
Category 2:
a. Drafting the manuscript
Supanut Apinyawasisuk
Xinkai Zhou
b. Revising it for intellectual content
Jack J. Tian
Giancarlo A. Garcia
Rustum Karanjia
Alfredo A. Sadun
Category 3:
a. Final approval of the completed manuscript
Supanut Apinyawasisuk
Xinkai Zhou
Jack J. Tian
Giancarlo A. Garcia
Rustum Karanjia
Alfredo A. Sadun

Background—Forced eyelid closure test (FECT) is a clinical screening test developed from the original Cogan lid twitch (CLT) sign to assist in the diagnosis of ocular myasthenia gravis (OMG), We evaluated the sensitivity and specificity of FECT compared to CLT and benchmarked to standard diagnostic tests.

Methods—This study was a retrospective chart review of 48 patients using electronic medical records of those that presented with ptosis and/or diplopia at Doheny Eye Institute, University of California, Los Angeles between February 2015 and April 2016. Patients without FECT testing were excluded. FECT and CLT results, and final diagnosis were recorded. To perform FECT, the patient was asked to squeeze his or her eyelids shut for 5–10 seconds then open quickly and fixate in primary position. The excessive upwards overshoot of eyelids movement indicated a positive FECT. The test was performed by a neuro-ophthalmologist prior to establishing the diagnosis. Patients who had equivocal test results and/or inconclusive final diagnosis were excluded.

Results—Of the 48 patients studied, 18 patients (37.5%) had positive FECT; 15 of whom had a final diagnosis of OMG (83.3%). Of the 30 patients with negative FECT, 1 had OMG (3.3%). Of the 48 patients, 35 patients also had a documented CLT result (72.9%). CLT was positive in 11 of these 35 patients (31.4%), and 9 of these 11 had OMG (81.8%). Of the 24 patients with negative CLT, 2 of them had OMG (8.3%). Sensitivity and specificity of FECT were 94% and 91% (joint 95% confidence region: sensitivity × specificity = [0.70,1] × [0.75, 1]). The relative true positive fraction (rTPF) between FECT and CLT was 1.15; the relative false positive fraction (rFPF) was 1.31.

Conclusion—FECT is a simple clinical screening test with good sensitivity and specificity for OMG.

Keywords

forced eyelid closure test; Bienfang’s test; Cogan’s lid twitch; ocular myasthenia gravis

Patients with ocular myasthenia gravis (OMG) typically present with clinically fatigable ptosis and/or binocular diplopia (1). In general, non-invasive clinical tests such as lid fatigability, ice test, rest test, and Cogan’s Lid Twitch test (CLT) are helpful screening tools to guide further diagnostic testing for OMG. Commonly used and well-studied diagnostic studies include the edrophonium test, serum acetylcholine receptor antibody (AchR Ab), single fiber electromyography (SFEMG), and repetitive nerve stimulation (RNS). However, all diagnostic tests have varying levels of sensitivity and specificity (2).

In our clinic, forced eyelid closure test (FECT) routinely is performed in patients suspected of having OMG. This test was first described by Don C. Bienfang, MD, a neuro-ophthalmologist at Harvard Medical School, in 1982 possibly or earlier and was formerly named “Bienfang test”. The primary objective of our study was to evaluate whether FECT achieved a minimally acceptable sensitivity and specificity, both set to 0.8. A secondary objective was to compare the sensitivity and specificity of FECT to CLT.

Methods

We retrospectively reviewed the electronic medical records of patients who presented at our neuro-ophthalmology clinic at Doheny Eye Institute, University of California, Los Angeles from February 2015 to April 2016, with ptosis or binocular diplopia as a chief complaint. We included all patients who were tested with FECT and had test results available. To perform the test, the patient was asked to tightly squeeze his or her eyelids shut for 5–10 seconds then open quickly and fixate at a target positioned in primary gaze. The observer sat 2–3 feet in front of the patient at the same eye level and immobilized the eyebrows with digital pressure to minimize the contribution of the frontalis muscle. A positive test was defined by an excessive upward overshoot of the eyelid upon opening followed by a downward drooping to arrive at the final position (Fig 1) (video). The test was performed by an experienced neuro-ophthalmologist (AAS). In addition, we collected the CLT result. To perform CLT, the patient was asked to look downward for at least 10 seconds and rapidly return to primary gaze. Excessive upward eyelid movement followed by downward drooping was considered a positive CLT.

The final diagnosis of each patient was recorded. The diagnosis of OMG was made when at least one of the standard diagnostic tests for myasthenia gravis was positive. These included edrophonium test, AchR Ab, muscle-specific receptor tyrosine kinase, single fiber EMG, repetitive nerve stimulation. Since these tests have varying levels of sensitivity for OMG, patients with negative diagnostic test results received an OMG diagnosis if they demonstrated clinical characteristics highly specific for OMG such as dramatic responsiveness to oral pyridostigmine or were later documented to progress to generalized myasthenia gravis. The results of FECT and CLT were not used for establishing the final diagnosis. Exclusion criteria were: patient with equivocal test results, and inconclusive final diagnosis. The study protocol was approved by the University of California, Los Angeles Institutional Review Board. Informed consent was exempted for this retrospective review.

Statistical Analysis

FECT and CLT results were cross-classified by OMG diagnosis in Table 1; true positive fraction (TPF) and false positive fraction (FPF) were calculated. We took $TPF = Sensitivity$ and $FPF = 1–Specificity$, and we used TPF and FPF for the analysis.

For the first objective, whether FECT achieves minimally acceptable sensitivity and specificity (both set to 0.8), we formulated a joint hypothesis that simultaneously test both parameters (3). The null hypothesis is H_0:{$TPF \leq 0.8$ *or* $FPF \geq 0.2$} and weperformed hypothesis testing by constructing a joint 95% confidence region for the pair (TPF, FPF). We reject the null hypothesis at 0.05 level if the confidence region lies entirely in the rejection region {$TPF \in (0.8,1]$ *and* $FPF \in [0,0.2)$}.

For the second objective, comparing FECT with CLT, we performed hypothesis testing on relative true positive fraction (rTPF) and relative false positive fraction (rFPF), calculated as $rTPF(FECT,CLT) = TPF(FECT)/TPF(CLT)$ and $rFPF(FECT,CLT) = FPF(FECT)/FPF(CLT)$. The model for TPF is $\log(TPF) \sim \alpha_0 + \alpha_1 \cdot Test$ where "*Test*" is a binary covariate that equals 0 for CLT and 1 for FECT, such that $\exp(\alpha_1) = rTPF(FECT,CLT)$. The model for FPF

is similar. Model coefficients were estimated by the Generalized Estimating Equations (GEE)(4) to allow for correlations between test results from the same subject. Table 2(a) summarizes estimated *rTPF*(*FECT,CLT*) and its 95% CI; Table 2(b) summarizes *rFPF*(*FECT,CLT*) results. The advantage of the above approach is that it allows us to use data from all 48 patients to obtain more efficient estimates of TPF and FPF for FECT, even though the CLT test results are not available for 13 of them. As a sensitivity analysis, we also peformed McNemar's test for TPF and FPF on the 35 subjects who have test results for both FECT and CLT.

Results

Electronic medical records of 57 patients initially were reviewed. One patient was excluded from the study due to an equivocal result for FECT and 8 patients were excluded due to inconclusive diagnosis. A total of 48 patients were included. Eighteen of these 48 patients (37.5%) demonstrated a positive FECT. Of the 18 patients, 15 patients (83.3%) had a final diagnosis of OMG. Of the 30 patients with negative FECT, 1 had OMG (3.3%). Of the 48 patients, 35 patients (72.9%) had an available CLT result. CLT was positive in 11 of 35 patients (31.4%), 9 of whom had a final OMG diagnosis (81.8%). Of the 24 patients with negative CLT, 2 patients had OMG (8.3%). The estimate TPF of FECT was 0.94 (94% sensitivity) and FPF was 0.09 (91% specificity) with joint 95% confidence region: TPF × FPF = [0.70,1] × [0, 0.25] (Fig E1). The estimated TPF of CLT was 0.82 (82% sensitivity) and FPF was 0.08 (92% specificity). To compare FECT to CLT, the rTPF was 1.15; the rFPF was 1.31. However, the results were not statistically significant at the 0.05 level for either TPF or FPF (Table 2). We reached the same conclusion from the sensitivity analysis that used the McNemar's test. Final diagnosis and clinical presentations of patients in positive and negative FECT groups are shown in Table 3.

Discussion

This is the first study evaluating the validity of FECT as a clinical diagnostic test for OMG. FECT provides high sensitivity and specificity for OMG diagnosis. However, comparison of FECT with CLT showed no statistically significant difference. Previous studies assessing CLT (5–7) showed trends toward low sensitivity (50% to 75%) and high specificity (91.7% to 100%) when compared to standard diagnostic tests, and the CLT results from the present study are in agreement. However, comparison of our sensitivity and specificity of CLT to the results of prior studies is limited due to different study populations.

The explanation for eyelid phenomenon in both FECT and CLT remains unproven. In 1965, Cogan (8) first introduced CLT as a characteristic eyelid sign of myasthenia gravis and proposed fatigability followed by increased gain and then a rapid recovery of extraocular muscles including LPS as an explanation for this phenomenon. When the patient's eyes return to primary position after the period of LPS relaxation on downgaze, the eyelid shoots upward excessively for a brief moment exposing the upper limbus due to rapid recovery of Ach levels in the context of compensatory gain before returning to resting position, and appears as a twitch. To further explain the phenomenon, we speculate that during the relaxation period, acetylcholine level builds up in the pre-synaptic junction of the nerve

terminal prior to being released and then activates the remaining acetylcholine receptors free from blockage by auto-antibodies at the post-synaptic junction of the LPS. The over-activated LPS contracts and excessively lifts the eyelid. The eyelid phenomenon in FECT can be demonstrated even in patients without ptosis (Fig 1).

Although comparison of FECT with CLT showed no statistical significance in regards to sensitivity and specificity, we believe that FECT might have a greater sensitivity than CLT. This is supported by 2 possibilities. First, the contraction of OO (main eyelids protractor) during forced eyelid closure performed in FECT allows full relaxation of LPS (main eyelid retractor, OO's antagonist) whereas sustained downgaze performed in CLT only allows partial LPS relaxation. This allows for a greater upward drift when LPS subsequently contracts. Second, there may be OMG-related fatiguing of OO. In both situations, the balance of LPS and its antagonist (OO) is altered in favor of LPS allowing momentary recovery. This recovery is short lived as LPS fatigues and the compensatory extra gain passes and the lid comes down again.

The false negative rate of FECT was low in our study. Among 16 patients in the OMG group, only 1 had a false negative FECT. The final diagnosis was confirmed by 2 diagnostic tests (AchR Ab and RNS). At the time this false negative FECT was performed, the patient had been treated elsewhere with pyridostigmine and oral corticosteroids.

Our study population contained 3 false positive FECTs. Among those 3 patients, two were diagnosed with Lambert-Eaton myasthenic syndrome (LEMS). Given that LEMS is an autoimmune disorder that affects neuromuscular transmission and associated fatigable extraocular muscle weakness (9), it comes as no surprise that a positive FECT can be expected in this condition. Other clinical signs of OMG, including enhanced ptosis and CLT also have been reported in LEMS (9, 10). Since the principle underlying both FECT and CLT is based on abnormality of acetylcholine level and AchR function, a positive FECT would possibly be expected in any disorder of neuromuscular transmission, including other myasthenic syndromes.

There were a number of limitations to our study. First, the sample size was too small to obtain statistically significant TPF and FPF. Second, CLT was not performed on all the patients. Third, the examiner was not completely masked to the patient's symptoms and/or diagnosis before performing the test. Fourth, the positivity and negativity of FECT was determined by an experienced neuro-ophthalmologist. Inexperienced observers might not be able to make a decision whether the test is positive or negative. Since this is a pilot study, a prospective, masked study should be performed with a large sample size and more observers with varying levels of experience. Moreover, inter-observer reliability needs to be addressed in any future study. There is some ascertainment bias from the exclusion of uncertain results in our study. Some of the excluded patients had positive FECT but the diagnosis of OMG could not be established for a number of reasons.

In conclusion, forced eyelid closure test, formerly called Bienfang's test is a simple, quick, non-invasive test and should be used as a valuable screening tool for OMG. Compared with CLT, it is non-inferior with regards to sensitivity and specificity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We want to acknowledge Professor Don C. Bienfang at Harvard Medical School for inventing the test and Shellee Rockwell (Doheny Eye Institute) for help in data collection.

References

1. Kupersmith MJ, Ying G. Ocular motor dysfunction and ptosis in ocular myasthenia gravis: effects of treatment. Br J Ophthalmol. 2005; 89:1330–1334. [PubMed: 16170126]
2. Benatar M. A systematic review of diagnostic studies in myasthenia gravis. Neuromuscul Disord. 2006; 16:459–467. [PubMed: 16793269]
3. Pepe, MS. The statistical evaluation of medical tests for classification and prediction. New York: Oxford University Press; 2003.
4. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. Biometrics. 1986; 42:121–130. [PubMed: 3719049]
5. Mittal MK, Barohn RJ, Pasnoor M, McVey A, Herbelin L, Whittaker T, Dimachkie M. Ocular myasthenia gravis in an academic neuro-ophthalmology clinic: clinical features and therapeutic response. J Clin Neuromuscul Dis. 2011; 13:46–52. [PubMed: 22361625]
6. Singman EL, Matta NS, Silbert DI. Use of the Cogan lid twitch to identify myasthenia gravis. J Neuroophthalmol. 2011; 31:239–240. [PubMed: 21654336]
7. Van Stavern GP, Bhatt A, Haviland J, Black EH. A prospective study assessing the utility of Cogan's lid twitch sign in patients with isolated unilateral or bilateral ptosis. J Neurol Sci. 2007; 256:84–85. [PubMed: 17374543]
8. Cogan DG. Myasthenia Gravis: A review of the disease and a description of lid twitch as a characteristic sign. Arch Ophthalmol. 1965; 74:217–221. [PubMed: 14318498]
9. Young JD, Leavitt JA. Lambert-Eaton Myasthenic Syndrome: Ocular Signs and Symptoms. J Neuroophthalmol. 2016; 36:20–22. [PubMed: 25993122]
10. Brazis PW. Enhanced ptosis in Lambert-Eaton myasthenic syndrome. J Neuroophthalmol. 1997; 17:202–203. [PubMed: 9304536]

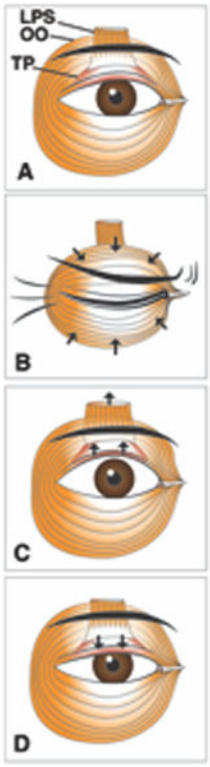

Figure 1.

Forced eyelid closure test. A series of schematic drawings illustrates activities of the right levator palpebrae superioris (LPS), tarsal plate (TP) and orbicularis oculi (OO). During the squeezing step (B), OO tensely contracts while LPS fully relaxes. Upon immediate eyelid opening (C), the balance of LPS and its antagonist (OO) is altered in favor of LPS (due to fatiguing of OO) allowing momentary recovery. This recovery is short lived as LPS fatigues and the compensatory extra gain passes and the lid comes down again (D).

Table 1

Cross-classification of FECT and CLT results by OMG diagnosis

	OMG			Non-OMG		
	CLT −	**CLT +**	**CLT ND**	**CLT −**	**CLT +**	**CLT ND**
FECT −	0	0	1	20	1	8
FECT +	2	9	4	2	1	0

FECT, forced eyelid closure test; CLT, Cogan lid twitch; OMG, ocular myasthenia gravis; −, negative; +, positive; ND: Not Done

Table 2

Regression model fit for FECT and CLT results using (a) the model for TPF and (b) the model for FPF.

(a)

Covariate	Estimate	rTPF (FECT, CLT)	95% CI
Constant	−0.20	–	–
Test (FECT vs CLT)	0.14	1.15	[0.84, 1.56]

(b)

Covariate	Estimate	rFPF (FECT, CLT)	95% CI
Constant	−2.63	–	–
Test (FECT vs CLT)	0.27	1.31	[0.26, 6.54]

FECT, forced eyelid closure test; CLT, Cogan's lid twitch; rTPF, relative true positive; rFPF, relative false positive fraction

Table 3

Clinical findings and final diagnosis of patients with positive and negative FECT

	Positive FECT	Negative FECT
Number of patients	18	30
Ptosis	17	14
Diplopia	16	25
Final diagnosis (N)	OMG (15) LEMS (2) Decompensated phoria (1)	Cranial nerve palsy (8) Decompensated phoria (6) Aponeurotic ptosis (5) TAO (2) CPEO (2) Skew deviation (2) Horner's syndrome (1) Mechanical strabismus (1) Convergence insufficiency (1) Orbital myositis (1) Dural AVF (1) HZO (1) MFS (1) OMG (1)

FECT, forced eyelid closure test; OMG, ocular myasthenia gravis; LEMS, Lambert-Eaton myasthenic syndrome; TAO, thyroid associated ophthalmopathy; CPEO, chronic progressive external ophthalmoplegia; AVF, arteriovenous fistula; HZO, herpes zoster ophthalmicus; MFS, Miller Fisher of Guillian-Barré syndrome