Eliciting Latent Myasthenia Gravis Eye Signs Utilizing 'The Mary Walker Effect'

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ABSTRACT

Current standardized tests to induce fatigability in the Myasthenia Gravis (MG) patient do not take into consideration that, in real-world situations, the patient is using more than one muscle group at a time. In 1895, the German physician Frederick Jolly, who is famed for coining the name Myasthenia Gravis, observed that exhaustion of one group of voluntary muscles in a patient with MG induced weakness in other groups that had not been stimulated. This phenomenon was also noted by Dr. Mary Walker and was named the Walker effect in 1938. The Novel ocular motility technique described in this paper is designed to engage the extraocular muscles (EOM) simultaneously with another muscle group namely the facial muscles, specifically testing for lip weakness. This test was named The SLOW Test (Simultaneous Lip and Ocular Weakness). It was found that observable Myasthenia Gravis Eyes Signs (MGES) were quicker to elicit and more obvious when performing the SLOW Test. The SLOW Test is a method designed to confirm the presence of MG signs quickly and effectively, even when there appear to be no obvious fatigable signs with current testing regimes. The test combines 'old knowledge' by testing for the 'Mary Walker Effect' with current ophthalmic testing for MG, which increases fatigue and allows for a higher suspicion level of generalized MG as another muscle group is simultaneously tested. The development of clinical methods for identifying latent fatigable muscle weakness is critical to reducing the cases of missed MG diagnosis, testing methods such as the SLOW Test have the potential to improve patients' quality of life by enabling earlier diagnosis and initiating earlier treatment.

KEYWORDS: Myasthenia Gravis, Neuromuscular Junction (NMJ), 'The Mary Walker Effect', Ocular Motility, Ptosis, Fatigability, Functional Neurologic Disorder (FND)

Introduction

Acquired Autoimmune Myasthenia Gravis (MG), is a potentially fatal, chronic neuromuscular disease caused by impaired synaptic transmission across the neuromuscular junction resulting in fatigable weakness that can range in severity from mild ocular muscle weakness to severe respiratory failure. MG is a serious disease and can present clinically with very severe symptoms in many patients; however, patients may present clinically with less weakness than they describe in their daily lives, as the intensity of the weakness in MG is variable even within the same patient on the same day and may include periods of complete resolution.[1]

Fatigable weakness in MG can range in severity from mild ocular muscle weakness to severe respiratory failure. However, even patients who are considered to have mild eye symptoms may be suffering from troubling symptoms that are dismissed, as their clinical ocular assessment may appear normal at the time of consultation. Patients who complain of symptoms such as dizziness, blurriness, and even diplopia in the absence of clinical signs are often dismissed or diagnosed as having another condition, for example, Functional Neurologic Disorder (FND).

It has long been known that MG patients can experience symptoms even when there is no obvious discernible clinical evidence. This phenomenon, however, remains poorly understood.[2] Recent video-based eye-tracking studies were able to detect such subclinical eye movements in MG patients who had symptoms without obvious ocular misalignment.[2] These studies highlight the limitations of current methods of clinical diagnosis of MG in observing subtle eye signs.

The eye muscles are the most susceptible muscle group to an autoimmune-mediated attack on the neuromuscular junction (NMJ) and, therefore, accurate ophthalmic examination is vital to aid in an early diagnosis.[3] However, as MG patients have quite variable responses to current methods of attempting to induce muscle fatigability, diagnosis in many patients may be delayed by many months or even years.[4]

The development of clinical methods for identifying latent fatigable muscle weakness is critical to reducing the cases of missed MG diagnosis. The novel ocular motility technique described in this paper is designed to engage the extraocular muscles (EOM) simultaneously with another muscle group to identify patients with MG who present with subtle eye signs or no discernible clinical eye signs. This method was developed based on the 'Mary Walker Effect' and increases fatigue, allowing for a higher suspicion level of generalized MG as another muscle group is simultaneously tested.

Background

Ophthalmic Signs in MG

MG can be easy to diagnose when there are obvious fatigable eye signs, however, it may present with variable OM restrictions that can mimic a variety of conditions or MG patients may complain of dizziness, unsteadiness, or blurring of vision in the absence of clinical eye signs. Some MG patients have fluctuating and fleeting ocular signs and

symptoms, for example, ptosis has been known to switch from one eye to the other, lasting only a few seconds.[4] At times, ptosis may not be obvious and may appear as a narrow palpebral fissure in one eye with upper lid retraction in the contralateral eye.[5]

The key to MG clinical diagnosis is inducing objective fatigable muscle weakness, however, many clinical tests fail to induce muscle weakness within the time constraints of regular consultation. Current testing for MGES involves a variety of standard tests to disclose MGES, such as ptosis, lid retraction, restriction of ocular movement, distinct saccadic signs, and orbicularis oculi weakness. The standard procedure for testing for MGES involves sustained gaze holding in elevation and also in lateral gaze. However, the results are often fleeting and not readily replicated.

Facial weakness in MG and the patient's difficulty with smiling

MG patients with orofacial weakness may complain of stiffness of the face and weakness of the lips, which can cause variable vertical smile, or 'myasthenic snarl' associated with abnormal fatigability on exertion. This aspect of MG is important to be aware of, as such a patient may appear depressed due to the weakness causing a downturned mouth. These patients tend to have a flat, expressionless face, which can severely affect a patient's quality of life by interfering with social interactions and employment opportunities.[6] However, obvious MG mouth weakness may not always be apparent at the time of the clinical examination and disclosing such weakness when the sign is latent is not only helpful for diagnosis but also allows for a greater understanding of the patient's lived experience with MG.

MG fatigue versus fatigability

An MG patient may appear strong and not display easily observable evidence of weakness on clinical examination, however their symptoms during daily life may be significant. Current standardized tests to induce fatigability in the MG patient do not take into consideration that in real-world situations the patient is using more than one muscle group at a time.

Distinguishing between 'fatigue' and 'fatigability' is crucial in MG diagnosis. 'Fatigue' is a subjective description of excessive tiredness or exhaustion that often interferes with activities of daily living (ADL). Whereas 'Fatigability' is an objective reduction in the strength of muscle groups after a specific action. A study by Barnett, C., et al. 2014 reinforces the importance of understanding impairment in MG and the mechanism of fatigability of muscle weakness. It discusses how an inadequate clinical assessment leads to the assumption that a patient might seem stronger over their daily activities than the reality of their difficulties with ADL,[7] which leads to misdiagnosis and subsequently a poor quality of life for the undiagnosed and untreated patient.

Development of a test to disclose latent fatigable muscle weakness in MG

The development of clinical methods for identifying latent fatigable muscle weakness is critical to reducing the cases of missed MG diagnosis. This paper presents a new method of inducing fatigable eye muscle weakness in MG by incorporating the 'Mary Walker Effect' – shown when wearing out one muscle group causes fatigue in other muscle groups.

The Mary Walker Effect

In 1895, the German physician Frederick Jolly, who is famed for coining the name Myasthenia Gravis, observed that exhaustion of one group of voluntary muscles in a patient with MG induced weakness in other groups that had not been stimulated. This phenomenon was also noted by Dr. Mary Walker and was named the Walker Effect in 1938.[8,9]

Mary Walker was most notably known for discovering that physostigmine and Prostigmin temporarily restored muscle function in patients with MG.[10] This discovery formed the basis for pyridostigmine (Mestinon) being used as a primary symptomatic treatment for MG, even today. and was her famous single case study trial that is considered one of the "greatest clinical observations of the twentieth century."[11]

The clinical sign known as 'the Mary Walker effect' was introduced after another study on two approximately equally severe MG patients who had been treated with Prostigmin. The patients exercised their forearm, whilst a tourniquet was applied and inflated to 200 mm Hg, secured at the elbow. While the pressure was applied to the cuff no weakness was noted in any other muscles, however approximately one minute after the pressure was released the eyelids began to droop, and after two minutes there was widespread weakness. Subsequent studies showed that when less forearm fatigue was induced the weakness in other muscles was much less following release of the cuff.[10]

The development of the new test described in this current paper combines the old knowledge of The Mary Walker Effect with current testing methods known to elicit MEGS today. Considering the variability in signs and symptoms in all MG patients, it is expected that responses will vary, however, it is hypothesized that observable fatigability will be increased by combining current MG examination techniques with The Mary Walker Effect.

Simultaneous Lip & Ocular Weakness (SLOW)

The SLOW Test was designed based on 'the Mary Walker Effect,' eyes and lip muscle combination was demonstrated in this report as the eyes have been shown to be the most susceptible muscle group to an autoimmune-mediated attack on the NMJ[3] and orofacial muscle weakness gives a distinct myasthenic facial appearance, as

the corners of the mouth droop downwards with fatigue.[6] This combination of muscles is effective as the fatigability of the lip muscle can be easily observed by the examiner whilst simultaneously examining the eyes. The acronym SLOW (Simultaneous Lip & Ocular Weakness) was chosen as it also is a reminder of the importance of performing ocular motility testing slowly.

The SLOW Test consists of asking the patient to 'smile while showing their teeth' thereby raising their upper lip and maintaining this position whilst slowly following a target and maintaining sustained gaze holding in elevation and then in lateral gaze. This ocular motility component of the test is performed as per the standard currently used testing method for eliciting MGES. This procedure results in simultaneously fatiguing two separate muscle groups, invoking the Mary Walker Effect.

The aim of this test is not to over-fatigue the patient but to see whether there is a noticeable weakness of the lip during a 15 – 30 second sustained smile associated with observable fatigable MGES with sustained gaze holding. Weakness of the lip is observable as 'falling' of the upper lip gradually worsening to a downward-facing mouth.

Tests for MGES can be done whilst watching for lip fatigue by questioning the patient about diplopia, or observing an MGES, e.g. sustained elevation or sustained lateral gaze looking for fatigability of eyelids and/or extraocular muscles gaze restriction, ptosis, or lid retraction.

Case Presentation

The patient demonstrating this phenomenon was a 51-year-old female with seronegative, single fiber electromyography (SFEMG) and repetitive nerve stimulation (RNS) positive, Mestinon positive, generalized MG (GMG). At the time of testing, the patient's generalized MG symptoms were well controlled on a combination of Mestinon, Methotrexate, Imuran, intravenous immunoglobulin (IVIG), adequate rest periods throughout the day, sufficient nightly sleep, lifestyle factors to reduce positive and negative stress, reduction and modification of activity levels dependent on MG symptoms. During MG exacerbations her symptoms included variable eye, bulbar and other generalized symptoms of MG, including breathing difficulties.

Variable MGES for this patient were elicited in different directions of gaze while performing the Slow Test including restriction of EOMs with diplopia, upper lid retraction, Cogan's Lid Twitch, lid hoping, lower lid retraction, unilateral ptosis on lateral gaze and bilateral ptosis on upgaze. The eliciting of any known MGES faster than other test methods during the Slow Test is considered a positive Slow Test. Saccades and orbicularis weakness, weren't tested as a part of the Slow Test, however, this patient had previously displayed variable MGES for both.

MGES were even identifiable using the SLOW Test on days when she was asymptomatic and at peak Mestinon dose. This provides evidence of the high level of sensitivity and accuracy of the SLOW Test in the MG patient. The SLOW Test was performed at a variety of intervals after the Mestinon dose. It was observed that MGES could be identified at any period, however the patient's fatigue was sustained longer when tested at times when the Mestinon dose had worn off. The patient reported greater levels of fatigue when SLOW Test was performed outside of the peak Mestinon effect, which is between 3-4 hours after the 4 hourly dose was taken. This patient was tested for MGES in different directions of gaze, noting where the MGES occurred. It was found that observable MGES were quicker to elicit and more obvious when performing the SLOW Test than previous MGES testing. It was noted that the fatigable weakness associated with a positive SLOW Test remained while the patient maintained their gaze holding while simultaneously attempting to continue their raised lip position.

Discussion

The SLOW Test allows for greater reliability in the assessment of MG by more accurately representing the patient's symptoms outside of the clinical consultation. Fatigable muscle weakness in the patient was induced within 15 seconds and the MG-resulting lip and ocular signs were maintained on a sustained attempt at gaze holding combined with a sustained attempt to maintain a smile whilst showing teeth, but disappeared with a blink or movement away from the position of gaze that disclosed the MGES.

Diagnosis of MG can be quite easy when there are obvious classical signs present. However, specific testing is required to diagnose when there are only mild signs or unusual symptoms. Considering the variability in signs and symptoms in all MG patients, it is expected that responses to the SLOW Test will vary, however it is hypothesized that observable fatigability will be increased through the use of the Mary Walker Effect.

The SLOW Test is a method designed to confirm the presence of MG signs quickly and effectively, even when there appear to be no obvious fatigable signs with current testing regimes. The development of clinical methods for identifying latent fatigable muscle weakness is critical to reducing the cases of missed MG diagnosis. Testing methods such as the SLOW Test have the potential to improve patients' quality of life by enabling earlier diagnosis and initiating earlier treatment.

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The author is an Orthoptist, living with Generalized Myasthenia Gravis, diagnosed in 2016.

References

1. Daroff RB. Ocular Myasthenia. In: Kaminski HJ, editor. Myasthenia Gravis and Related Disorders. Totowa, NJ: Humana Press. ; 2003. doi:10.1007/978-1-59259-341-5_5.

2. Chisari CG, Sciacca G, Reggio E, Terravecchia C, Patti F, Zappia M. Subclinical involvement of eye movements detected by video-based eye tracking in myasthenia gravis. Neurological Sciences. 2023 2023/07/01;44(7):2555-2559. doi:https://doi.org/10.1007/s10072-023-06736-6.

3. Zhou Y, Kaminski HJ, Gong B, Cheng G, Feuerman JM, Kusner L. RNA expression analysis of passive transfer myasthenia supports extraocular muscle as a unique immunological environment. Invest Ophthalmol Vis Sci. 2014 Jun 10;55(7):4348-59. eng. Epub 20140610. doi:10.1167/iovs.14-14422. Cited in: Pubmed; PMID 24917137.

4. Layzer RP. Handbook of myasthenia gravis and myasthenic syndromes. Neurological disease and therapy. Vol. 37. New York: Marcel Dekker; 1995. 417-417 p. (Lisak RP, editor. Annals of Neurology; vol. 3). ISBN: 0364-5134. https://onlinelibrary.wiley.com/doi/abs/10.1002/ana.410370329.

5. Hake A, Kaminski HJ. Ocular Myasthenia Analysis of Diagnostic and Treatment Options. Huang F-P, editor.: Shanghai; 2011. (vol. Autoimmune Disorders). https://www.intechopen.com/books/autoimmune-disorders-current-concepts-and-advances-from-bedside-to-mechanistic-insights/ocular-myasthenia-analysis-of-diagnostic-and-treatment-options.

6. Weijnen FG, van der Bilt A, Wokke JH, Kuks JB, van der Glas HW, Bosman F. What's in a smile?: Quantification of the vertical smile of patients with myasthenia gravis. J Neurol Sci. 2000 Feb 15;173(2):124-8. eng. doi:10.1016/s0022-510x(99)00319-6. Cited in: Pubmed; PMID 10675656.

7. Barnett C, Bril V, Kapral M, Kulkarni A, Davis AM. A conceptual framework for evaluating impairments in myasthenia gravis. PLoS One. 2014;9(5):e98089. eng. materials. Epub 20140520. doi:10.1371/journal.pone.0098089. Cited in: Pubmed; PMID 24844418.

8. Keynes G. The history of myasthenia gravis. Medical history. 1961;5(4):313-326. doi:10.1017/s0025727300026612.

9. Nguyen-Cao TM, Gelinas D, Griffin R, Mondou E. Myasthenia gravis: Historical achievements and the "golden age" of clinical trials. Journal of the Neurological Sciences. 2019 2019/11/15/;406:116428. doi:https://doi.org/10.1016/j.jns.2019.116428.

10. Walker MB. Some discoveries on myasthenia gravis: the background. Br Med J. 1973 Apr 7;2(5857):42-3. eng. doi:10.1136/bmj.2.5857.42. Cited in: Pubmed; PMID 4572033.

11. Lee MR. The miracle at St Alfege's: seventy years on. J R Soc Med. 2007 Feb;100(2):108-9. eng. doi:10.1177/014107680710000230. Cited in: Pubmed; PMID 17277286.