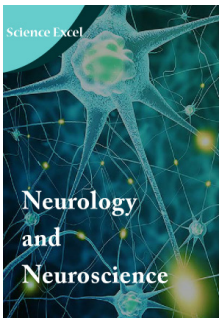
Neurology & Neuroscience

Original Article



Revisiting two clinical techniques for diagnosing myasthenia gravis in Covid times: Pointing to semiology

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- Received Date: 02 June 2021
- Accepted Date: 23 June 2021
- Publication Date 30 June 2021

Keywords: myasthenia gravis; covid pandemic; neuro-semiology; curtain-sign; mary-walker maneuver.

Abstract

As it has been evident in these times of the Covid-19 pandemic, the majority of health resources have been focused to the acute treatment, vaccination or research to this condition. By these reasons, some confirmatory complementary tests in many pathologies cannot be made or are postponed, including Myasthenia Gravis. Two clinical neurological signs useful for diagnosis of Myasthenia Gravis are revised: the "Curtain Sign" (also called paradoxical ptosis), that is evoked opening the more closed eye, which results in a dropping of the contralateral eyelid; and the Mary-Walker maneuver, which results from repetitive pronation-supination exercise under anaerobic conditions in one or both arms resulting in increasing of bilateral ptosis. The importance of a presumptive early diagnosis of Myasthenia Gravis is the early onset of specific treatment even when it's impossible to carry out complementary studies like single-fiber electromyography, thoracic images, or specific immune studies. .

Introduction

On March 11, 2020, the World Health Organization (WHO) declared SARS-Cov-19 a pandemic [1]; and the emergence of this condition has resulted in a great cost in health resources, with a global cost estimated in about 14% of worldwide 2019 gross domestic product [2], with a total vaccination financial costs amount to US$ 2.018 billion [3]. On the other hand, there has been evident temporary disruptions in routine and nonemergency medical care access, especially during periods of considerable community transmission of SARS-CoV-2 [4], degenerating in an obvious but undesirable increase morbidity and mortality risk associated with treatable and preventable health conditions [4,5] like hypertension, diabetes and diabetes related complications, cancer treatment and cardiovascular emergencies in 31% to 53% in different countries [5]. The diseases mentioned above are a public health problem, especially for their high frequency; but many other conditions with low prevalence and incidence like Myasthenia Gravis (MG), with prevalence rates about 14.2 to 20 per 100,000 in the US population [6,7], or incidence rates reported between 3.0 and 30.0/1,000,000/year [8], have not only seen their treatment postponed, but also their accurate and prompt diagnosis.

Diagnosing myasthenia gravis

The diagnosis of MG seems simple, since is based on a correct anamnesis, and is characterized by muscle weakness that fluctuates, worsening with exertion, and improving with rest [6] affecting ocular, bulbar and (proximal) limb skeletal muscle groups [9]. But in many cases, the correct diagnosis is delayed; for example, according to some reviews, only 54% to 69% of patients with MG are diagnosed within first year of symptoms onset, and the mean time to diagnosis is more than one year [7]; and as many reports have shown, many patients had initially been diagnosed with psychiatric disorders like depression [10]. Added to this, is the absence of clearly and validated diagnostic criteria for MG in literature.

Actually, it's know that the majority of physician use a mentally algorithm to make the diagnosis of MG: limb or ocular ptosis of fluctuating characteristic, followed by a electrophysiological evaluation, antibodies specific test, and thorax images studies; [9], but in a Covid pandemic scenario, a high pre-test suspicion is ideal to avoid contagion risk situations; and in developing countries, an early diagnosis of MG is essential to try to initiate a symptomatic treatment only based on the clinic, until the medical services normalize its operation.

This is the principal reason to do this mini-review: to highlight some techniques of the physical examination that help to make a more acute presumptive diagnosis of MG.

The best clinical assessment in MG diagnosis, is trying to demonstrate a striking fatigue, such as rapidly evolving ptosis during up gaze, eye drift on sustained lateral or vertical gaze, or profound dysarthria developing during history [11].

Citation: Vargas-Cañas A, Martínez A, Velásquez M, Guerrero R. Revisiting two clinical techniques for diagnosing myasthenia gravis in Covid times: Pointing to semiology. Neurol Neurosci. 2021; 2(2):1-3.

Mary-walker maneuver

One of the hallmark of MG suspicion is the fatigable ptosis; this sign should be evaluated with the patient sitting comfortably in a head primary position [7]. Then, the examiner ask the patient to fixate the gaze on a distant and upper object, and asks to refrain from blinking and to relax the forehead muscle during 30 seconds [7]; this causes increased ptosis. But, in many situations, the response is inconcludent. However, there is a maneuver that can enhance this clinical finding: the Mary-Walker Maneuver.

Mary Broadfoot Walker [12], was a Scottish physician recognized worldwide for the remarkable discovery of physostigmine treatment for MG in her thesis "A Contribution to the Study of Myasthenia Gravis" [13] and also for the description of "Mary-Walker effect", also called Mary-Walker Maneuver. On 1938, Walker presented a patient with MG and ptosis; at a time, the circulation is cut-off in both arms by inflating sphygmomanometer cuff to 200 mm Hg; then, the patient is asked to prone and supine the forearm until tiredness and pain on the forearm appear. The maneuver continues with the released of cuff pressure. After a latent period of one to two minutes, the eyelid drop increases [13] as seen in Figure 1. A variant with the same results is doing it only in a forearm.

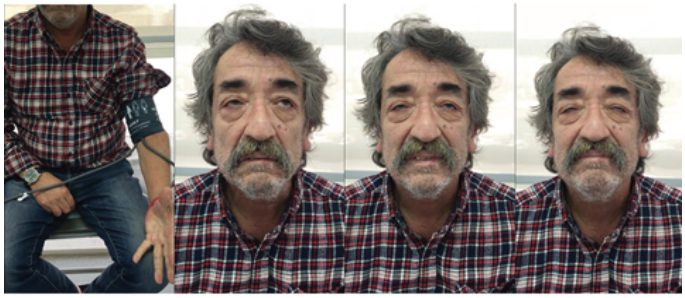

Figure 1. Mary-Walker Maneuver: Worsening of ptosis post-exercise in anaerobic condition, 01 minute after releasing the sphygmomanometer.

Although the humoral mechanism responsible remains open to speculation [2], Walker hypothesized that myasthenic muscles released a curarizing agent during activity, which entered the systemic circulation and blocked neuromuscular transmission at skeletal muscle motor endplates [13], however, our opinion is that it's associated with the effect of lactic acid accumulated in forearm, and then released into bloodstream: Lactate accumulation or metabolic acidosis, induced by short-duration, high intensity exercise during anaerobic models, increased concentrations of H+ ions, generating a decreased in pH, inhibition of PKF (phosphofrutokinase) enzyme, and reduction in glycolysis, resulting in an early fatigue process [14]. Although the literature still shows controversies regarding a direct relationship between acidosis and decrease in muscle strength as the only cause of fatigue in high intensity and short duration exercises, it can also be attributed to an accumulation of interstitial potassium added to the phenomenon previously described [14].

Curtain-sign

As it has been mentioned; a fatigable and fluctuating ptosis is a hallmark in myasthenic patients [7]; and typically, of notorious asymmetry [7,11]. This phenomenon originates a paradoxical face aspect, usually observed in patients with some initial degree of ptosis [7]. A technique useful to help us diagnose MG, is the "Curtain-Sign", or "paradoxical ptosis" [7] also named "enhanced ptosis" [15]. It's demonstrated during ocular upgaze in patients with bilateral ptosis by elevating and maintaining the more ptosic eyelid in a fixed position [7,15], as seen in Figure 2. The opposite eyelid slowly falls and may close completely. In some cases, the descending eyelid oscillates until the point of complete closure. During the maneuver, patients must be instructed to refrain from blinking [7,15]. The explanation of this phenomenon is support by Hering's law of equal innervation: the manual elevation of one droop palpebral decreases the effort for eyelid elevation ipsilateral and results in relaxation contralateral, thus leading to 'enhanced' ptosis [16].

A clinical sign, similar to the Curtain-Sign, is Cogan´s sign, described by David Cogan in 1965 [17]. This sign is elicited by instructing the patient to keep a downward gaze for 15 seconds and then asking to make an upward gaze [16-18]. In patients with a positive sign, the response is that the upper lid produces an upward twitch, or overshoot, once the patient has returned the gaze to the primary position [16]. This maneuver has, according to a study, a specificity of 99%, with a sensitivity of 75% and a false-positive rate of 1% [18]. A technique derived from Cogan´s Sign is the Forced Eyelid Closure Test (FECT). To perform the FECT, the patient is asked to squeeze his or her eyelids shut for 5-10 seconds, then it's ordered to open the eyes quickly and fixate in primary position [19]. This test was validated in a study with sensitivity and specificity of 94% and 91% respectively [19].

Figure 2. Curtain-Sign: In primary gaze position (a), the most ptosic eyelide is raised (b,c), with progressive increase in ptosis in the contralateral eyelid.

Myasthenia gravis and COVID

As mentioned previously, during Covid-19 pandemic, many diseases have been delayed in their diagnosis and treatment [5]; also many others have been triggered by the virus, as it was evidenced in many post Covid-19 patients who did present a new diagnosis of MG [20-22]; and would be explained due to the generation of autoantibodies against the neuromuscular junction [20], specifically due to a potential molecular mimicry between the acetylcholine receptor (AChR) and SARS-CoV-2 proteins that triggered the immune response leading the post-infectious onset of MG [21], explained because the antibodies that are directed against SARS-CoV-2 proteins may cross-react with AChR subunits, because the virus has epitopes similar to components of the neuromuscular junction [22].

On the other hand, it is clear that the SARS-CoV-2 infection can worsen MG patients in 50% according to a review report [23]. In those patients, a myasthenic crisis is highly probable due to the combination of reduced neuromuscular safety factors adversely affected by pyrexia and the effect of acute inflammatory mediators compounded by immunosuppression [24].

Discussion

As recently published by one of our authors, the power of observation, a logical anamnesis, and methodic physical examination, continues to be the basis in clinical neurology and is still the best way to an accurate neurological diagnosis [25]; the clinical examination or

maneuvers such as ice test, rest test, Tensilon test, among others, have better or at least best specificity or sensibility for MG diagnosis reaching 92% - 99% sensitivity and 91% to 97% of specificity in ocular MG versus 62% to 97%, and 73% to 96% sensitivity and specificity respectively for single-fiber electromyography in the same condition [26]. Regarding the two revised sings, we also want to point out that the Mary-Walker maneuver can also be performed in one arm with a positive result.

The Cogan´s sign, and the FECT technique, have also a specificity of 99%, with a sensitivity of 75% as mentioned previously [18], corroborating that neurology is a discipline characterized by the power of observation as an important skill in the richness of the semiology and the acuity of the neurological diagnosis [25]; and even the clinic criteria must be mandatory, and the complementary test serve as diagnostic support.

It is not easy to have, in outpatient scenario, Tensilon blisters or an ice pack to perform the Tensilon-test, or Ice test respectively. By this reason, we think that remembering techniques like Mary-Walker maneuver, or Curtain sign, would be useful in the early diagnosis of MG, especially in Covid time.

Conclusion

In developing countries, and even in first world countries, the Covid-19 pandemic has changed the way to provide health care to chronic non-communicable and low prevalence diseases like MG; for this reason, the acuity of the neurological examinations remains essential for an early diagnosis of this condition.

In this context, and due to the easy performing, we believe that the Curtain sign, and the Mary-Walker maneuver would be very useful in daily clinical practice in patients with suspected MG.

It would be recommendable; as with other maneuvers such as the Tensilon test, or the ice test; to perform studies to demonstrate the sensitivity and specificity of the Curtain sign, and the Mary-Walker maneuvers.

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