Neurological Sciences (2021) 42:4889–4892
https://doi.org/10.1007/s10072-021-05566-8

COVID-19

Myasthenia gravis and telemedicine: a lesson from COVID-19 pandemic

Dario Ricciardi[1] · Silvia Casagrande[2] · Francesco Iodice[3] · Bianca Orlando[3] · Francesca Trojsi[1] · Giovanni Cirillo[1,2,3,4] · Marinella Clerico[5] · Marco Bozzali[6,7] · Letizia Leocani[8,9] · Gianmarco Abbadessa[1] · Giuseppina Miele[1] · Gioacchino Tedeschi[1] · Simona Bonavita[1] · Luigi Lavorgna[1] · on behalf of the Digital Technologies, Web, Social Media Study Group of the Italian Society of Neurology

Received: 13 June 2021 / Accepted: 12 August 2021 / Published online: 26 August 2021

Abstract

COVID-19 pandemic has induced an urgent reorganization of the healthcare system to ensure continuity of care for patients affected by chronic neurological diseases including myasthenia gravis (MG). Due to the fluctuating nature of the disease, early detection of disease worsening, adverse events, and possibly life-threatening complications is mandatory. This work analyzes the main unresolved issues in the management of the myasthenic patient, the possibilities offered so far by digital technologies, and proposes an online evaluation protocol based on 4 simple tests to improve MG management. Telemedicine and Digital Technology might help neurologists in the clinical decision-making process of MG management, avoiding unnecessary in presence consultations and allowing a rational use of the time and space reduced by the pandemic.

Keywords Telemedicine · Tele-neurology · Tele-health · Myasthenia gravis · COVID-19

The pandemic coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV2), is still spreading around the globe and has raised serious concerns throughout the health system and severely limiting the access of patients with chronic diseases to the hospital setting [1, 2]. Since safety protection of both patients and healthcare workers has become the priority, restriction measures have led to a deep impact on patients' care and quality of life, particularly for those affected by chronic neurological disorders [3, 4]. Therefore, the pandemic fostered a quick reorganization of the healthcare system, particularly urgent as the virus's behavior and its aftermath in the next months are still unpredictable [5].

The pandemic had a significant impact on the management of patients with myasthenia gravis (MG). Management of MG includes the concepts of clinical surveillance, continuous treatment (as a chronic disease), and personalized/precision medicine. By these cornerstones, specific

Dario Ricciardi and Silvia Casagrande contributed equally to this work.

✉ Francesco Iodice
franc.iodice@gmail.com

1 I Division of Neurology and Neurophysiopathology, Department of Medical, Surgical, Neurological, Metabolic and Aging Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy

2 Department of Neuroscience, Psychology, Drug Research and Child Health (NEUROFARBA), University of Florence, Florence, Italy

3 Department of Neuroscience, San Raffaele Pisana IRCCS, via della Pisana 435, 00166 Rome, Italy

4 Division of Human Anatomy - Neuronal Networks Morphology Lab, Department of Mental, Physical Health and Preventive Medicine, University of Campania "Luigi Vanvitelli", Naples, Italy

5 Clinical and Biological Sciences Department, University of Torino, Orbassano, Italy

6 Department of Neuroscience, Brighton and Sussex Medical School, University of Sussex, Brighton, UK

7 Rita Levi Montalcini Department of Neuroscience, University of Torino, Turin, Italy

8 Department of Neurorehabilitation, IRCCS San Raffaele Hospital, Milan, Italy

9 University Vita-Salute San Raffaele, Milan, Italy

guidelines have recently focused on the clinical management of MG patients [6]. All treatment decisions should be individualized and made collaboratively between patients and healthcare providers. Patients should continue ongoing treatment monitoring blood markers and it is advised not to discontinue existing medications or initiate new treatments unless specifically discussed and approved by the healthcare providers, to reduce hospitalization and avoid the potential risk of increased disease activity and/or of MG crisis [7]. It is unclear whether COVID-19 causes more severe disease in patients with chronic neuromuscular disorders; a recent study suggests that the clinical course and outcomes in patients with MG and COVID-19 are highly variable, including reports of possible good outcomes [7–10]. However, due to the intrinsic fluctuating nature of the disease and the risk of exacerbation related to any viral or bacterial infections [11], MG patients, especially those already on immunosuppressive medications, are highly recommended to adhere to social distancing and restrictions, avoiding public gatherings and public transport and, where possible, using an alternative to face-to-face consultations, like telemedicine. MG patients constitute an exceptionally vulnerable group during the current COVID-19 pandemic due to multiple issues. First, they have a well-known risk of neurological exacerbations related not only to any viral or bacterial infections but also to drug exposure [11]. In fact, the treatment of COVID-19 includes the use of drugs advised by the International Consensus Guidance for Management of MG such as azithromycin and hydroxychloroquine [12] and other sedative and/or paralytic drugs necessary for intubation and ventilation [13]. Second, they could be at higher risk of COVID-19-related respiratory failure because of baseline respiratory weakness. At least, despite reassuring preliminary data regarding chronic immunosuppression and clinical outcome of COVID-19 [14, 15], further evidence is needed to rule out an additional risk for MG patients on chronic immunosuppressive therapies.

The pandemic was a worrying event for patients with MG: An online survey conducted in China showed that patients were very concerned about the COVID-19 pandemic and many have changed their lifestyle to reduce the risk of infection [16]. The direct relationship between COVID and myasthenic crises has not been fully elucidated although these may be exacerbated by infection and the use of IVIg could be a potential benefit for both [17]. In 15 consecutive adult MG patients admitted with COVID-19, 87% were admitted in the intensive care unit, 73% needed mechanical ventilation, and 30% died, suggesting a more severe course in this population [18].

To collect information about the outcome of patients with MG and COVID-9, the International MG/COVID-19 Working group has recently developed a physician-reported registry named CARE-MG: COVID-19 Associated Risks and Effects in Myasthenia Gravis. Preliminary data published in December 2020 reported an MG-worsening in 40% of patients and have higher mortality than the general population with COVID-19 [6].

The trend in recent studies is to implement telemonitoring and telemedicine facilities that could make health disease control efficient and better select those few people who have a hospital assessment [19]. In this scenario, the American Academy of Neurology (AAN) has urgently developed guidance for clinicians to implement telemedicine services amid the COVID-19 crisis [20]. However, the potential and limitations of telemedicine in the management of patients with myasthenia gravis are still almost completely unexplored and some key points must be understood as the spread of these techniques is destined to grow in the final tail of the pandemic and in the long phase of adjustment that will follow. Therefore, telemedicine and digital technologies (DT), through easy devices such as videoconference, might help physicians in the decision-making process and represent a new strategy to ensure the continuity of care.

Tele-neurology allows not only the protection of MG patients from potential exposure to COVID-19 but also closer clinical surveillance in the case of infection in a non-healthcare setting, essential for the possibility of a more rapid decline in respiratory function and of exacerbation of the underlying neuromuscular symptoms. Follow-up of stable patients with MG through telemedicine has been already considered by the expert of high utility/appropriateness during the COVID-19 pandemic [21].

Besides neurological examination, which is essential to detect signs of disease activity and an early deterioration of the clinical condition, validated clinical scales are very useful tools for disease monitoring with an acceptable rate of interrater reliability and reproducibility and include Myasthenia Gravis Foundation of America Clinical Classification (MGFA) Clinical Classification, Quantitative Myasthenia Gravis (QMG), and Myasthenia Gravis Activity of Daily living (MG-ADL) [22, 23].

MGFA helps to categorize individual cases according to a scale of progressive severity in five stages, from I (symptoms and signs narrowed to the ocular district) to the V stage (patient intubated with severe restrictive disventilatory pattern). QMG is a 13-item scale used for the assessment of signs and symptoms relative to ocular, cranial, respiratory, axial, and limb muscle function. The MG-ADL in an 8-item questionnaire regarding the impact of common MG symptoms in the activity of daily living. While QMG requires trained personnel and approximately 20 min to be completed, MGFA and MG-ADL do not require intensive training for physicians and their administration requires less than 5 min. Their ease of use and short lead times make these last two scales good candidates for use via telemedicine tools, as during a video call. Various maneuvers or tests

are routinely used in the clinical practice to investigate the presence of signs of fatigability; the core syndrome of MG might be easily translated to the context of telemedicine.

The most frequent and common signs/concerns of MG include ptosis and diplopia; however, these do not represent a "red flag" and a warring alarm. On the other hand, dysphagia, dysarthria, and dyspnea frequently represent signs of the unstable clinical condition and a potential clue of increased disease activity.

Besides bulbar symptoms, dysphagia may seem difficult to evaluate remotely, but swallow tele-evaluation has been demonstrated to have high accuracy and reliability in many different contexts [24–26] and the appropriateness of dysphagia assessment via telemedicine has been outlined by the World Muscle Society position papers about the management of patients with neuromuscular disorders during COVID-19 pandemic [22, 27].

Isolated reports investigated the use of questionnaires administered by telephone to monitor the clinical progress of patients and emerged that, on 45 people contacted, a worsening of respiratory functions demonstrated by telephone interview had a positive predictive power of more than 80% [28].

Based on literature analysis, we suggest a basic testing system to differentiate remotely patients according to disease severity and to identify patients at greater risk of myasthenic crisis. This is a 4-item test to quickly detect signs and symptoms of bulbar and respiratory involvement, the red flag for the need of face to face evaluation and, wherever appropriate, hospitalization:

a) Counting aloud (CAT): ask the patient to take a deep breath and count out loud as many numbers as they can. This simple test might enhance dysarthria (nasal, lingual, or labial) and results in dyspnea. Moreover, it gives an approximate idea of the vital capacity multiplying the number the patient can achieve with one breath by 100. The test is particularly simple and, for this reason, it can be performed safely via video consultation or even by telephone, providing an initial picture of any changes in the clinical picture [28].
b) Hoarseness test (HT): weakness of the laryngeal muscles results in *hoarseness*, namely changes in the voices. This can be elicited by asking the patient to make a high-pitched sound [29]. This test is also very simple and can be performed via telephone or video and can be performed by a trained caregiver who can help the doctor monitor small changes that require hospital re-evaluation.
c) Head up Test (HUT): while supine, ask the patient to flex the head and keep it flexed as long as they can (at least 10 s). Typically, neck flexion is weaker than neck extension in patients with MG and weakness of neck muscles is frequently related to fatigability of muscles with bulbar innervation. The dropping of the head is frequently associated with worsening of the clinical picture of MG [30] and can be examined by video consultation with the support of a caregiver who has been sufficiently trained in the administration of this test. A significant deterioration in the result of this simple test may be a reason for referring the patient to a hospital consultation.
d) Swallowing test (ST): the 3-oz swallowing test allows to evaluate the patient's swallowing abilities by observing the reaction to the swallowing of a small amount of water and defines the risk of ingestion through the loss of liquid, the appearance of cough, and changes in the voice [31]. This last parameter may reveal, in particular, a subacute worsening of the function of the laryngeal muscles associated with a myasthenic crisis. The evaluation can be performed by a well-trained caregiver and offer the possibility to quickly and non-invasively assess changes in swallowing function and send to hospital consultation only the most suspected cases for a clinical worsening.

In conclusion, telemedicine can offer valid support in (a) detecting early symptoms and signs of disease worsening, (b) preventing life-threatening complications, and (c) highlighting early changes in the clinical picture that requires to be evaluated in a hospital setting. We acknowledge that *tele-neurology* has many limitations but we emphasize that implementing the telemedicine approach for patients with MG is necessary to improve patients' management during the COVID-19 pandemic.

Author contribution All authors have reviewed and approved the contents of the manuscript and have read and understood the journal's ethical statement.

Declarations

Ethical approval None.

Conflict interest The authors declare no competing interests.

References

1. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. https://www.who.int/directorgeneral/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020
2. Buonsenso D, Iodice F, Sorba Biala J, Goletti D (2021) COVID-19 effects on tuberculosis care in Sierra Leone. Pulmonology 27:67–69. https://doi.org/10.1016/j.pulmoe.2020.05.013
3. Brigo F, Bonavita S, Leocani L et al (2020) Telemedicine and the challenge of epilepsy management at the time of COVID-19

pandemic. Epilepsy Behav 110:107164. https://doi.org/10.1016/j.yebeh.2020.107164
4. Moccia M, Lanzillo R, Brescia Morra V et al (2020) Assessing disability and relapses in multiple sclerosis on tele-neurology. Neurol Sci 41:1369–1371. https://doi.org/10.1007/s10072-020-04470-x
5. Bonavita S, Tedeschi G, Atreja A, Lavorgna L (2020) Digital triage for people with multiple sclerosis in the age of COVID-19 pandemic. Neurol Sci 41:1007–1009. https://doi.org/10.1007/s10072-020-04391-9
6. International MG/COVID-19 Working Group, Jacob S, Muppidi S et al (2020) Guidance for the management of myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS) during the COVID-19 pandemic. J Neurol Sci 412:116803. https://doi.org/10.1016/j.jns.2020.116803
7. Anand P, Slama MCC, Kaku M et al (2020) COVID-19 in patients with myasthenia gravis. Muscle Nerve. https://doi.org/10.1002/mus.26918
8. Rein N, Haham N, Orenbuch-Harroch E et al (2020) Description of 3 patients with myasthenia gravis and COVID-19. J NeurolSci 417. https://doi.org/10.1016/j.jns.2020.117053
9. Hübers A, Lascano AM, Lalive PH (2020) Management of patients with generalised myasthenia gravis and COVID-19: four case reports. J Neurol Neurosurg Psychiatry 91:1124–1125. https://doi.org/10.1136/jnnp-2020-323565
10. Ramaswamy SB, Govindarajan R (2020) COVID-19 in refractory myasthenia gravis—a case report of successful outcome. J Neuromuscul Dis 7:361–364. https://doi.org/10.3233/JND-200520
11. Gummi RR, Kukulka NA, Deroche CB, Govindarajan R (2019) Factors associated with acute exacerbations of myasthenia gravis. Muscle Nerve 60:693–699. https://doi.org/10.1002/mus.26689
12. Narayanaswami P, Sanders DB, Wolfe G et al (2021) International consensus guidance for management of myasthenia gravis: 2020 update. Neurology 96:114–122. https://doi.org/10.1212/WNL.0000000000011124
13. Meng L, Qiu H, Wan L et al (2020) Intubation and ventilation amid the COVID-19 outbreak: Wuhan's experience. Anesthesiology 132:1317–1332. https://doi.org/10.1097/ALN.0000000000003296
14. Kovvuru S, Nalleballe K, Onteddu SR et al (2021) Immunosuppression in chronic autoimmune neurological disorders during the COVID-19 pandemic. J Neurol Sci 420.https://doi.org/10.1016/j.jns.2020.117230
15. Andersen KM, Mehta HB, Palamuttam N et al (2021) Association between chronic use of immunosuppresive drugs and clinical outcomes from coronavirus disease 2019 (COVID-19) hospitalization: a retrospective cohort study in a large US health system. Clin Infect Dis.https://doi.org/10.1093/cid/ciaa1488
16. Li Y, Emmett CD, Cobbaert M et al (2021) Knowledge and perceptions of the COVID-19 pandemic among patients with myasthenia gravis. Muscle Nerve 63:357–364. https://doi.org/10.1002/mus.27130
17. Delly F, Syed MJ, Lisak RP, Zutshi D (2020) Myasthenic crisis in COVID-19. J Neurol Sci 414:116888. https://doi.org/10.1016/j.jns.2020.116888
18. Camelo-Filho AE, Silva AMS, Estephan EP et al (2020) Myasthenia gravis and COVID-19: clinical characteristics and outcomes. Front Neurol 11:1053. https://doi.org/10.3389/fneur.2020.01053
19. Roy B, Nowak RJ, Roda R et al (2020) Teleneurology during the COVID-19 pandemic: a step forward in modernizing medical care. J Neurol Sci 414:116930. https://doi.org/10.1016/j.jns.2020.116930
20. Telehealth and Remote Care. https://www.aan.com/tools-and-resources/practicing-neurologists-administrators/telemedicine-and-remote-care/. Accessed 7 Feb 2021
21. Guidon AC, Amato AA (2020) COVID-19 and neuromuscular disorders. Neurology 94:959–969. https://doi.org/10.1212/WNL.0000000000009566
22. Bedlack RS, Simel DL, Bosworth H et al (2005) Quantitative myasthenia gravis score: assessment of responsiveness and longitudinal validity. Neurology 64:1968–1970. https://doi.org/10.1212/01.WNL.0000163988.28892.79
23. Wolfe GI, Herbelin L, Nations SP et al (1999) Myasthenia gravis activities of daily living profile. Neurology 52:1487–1489. https://doi.org/10.1212/wnl.52.7.1487
24. Ward EC, Sharma S, Burns C et al (2012) Validity of conducting clinical dysphagia assessments for patients with normal to mild cognitive impairment via telerehabilitation. Dysphagia 27:460–472. https://doi.org/10.1007/s00455-011-9390-9
25. Morelli N, Rota E, Terracciano C et al (2020) The baffling case of ischemic stroke disappearance from the casualty department in the COVID-19 era. ENE 1–3.https://doi.org/10.1159/000507666
26 Penner JL, McClement SE, Sawatzky J-AV (2007) Management of dysphagia in advanced oropharyngeal cancer. Int J Palliat Nurs 13:206–212. https://doi.org/10.12968/ijpn.2007.13.5.23498
27. Guidon AC, Muppidi S, Nowak RJ et al (2021) Telemedicine visits in myasthenia gravis: expert guidance and the Myasthenia Gravis Core Exam (MG-CE). Muscle Nerve.https://doi.org/10.1002/mus.27260
28. Kukulka K, Gummi RR, Govindarajan R (2020) A telephonic single breath count test for screening of exacerbations of myasthenia gravis: a pilot study. Muscle Nerve 62:258–261. https://doi.org/10.1002/mus.26987
29. Larson ST, Wilbur J (2020) Muscle weakness in adults: evaluation and differential diagnosis. Am Fam Physician 101:95–108
30. Sih M, Soliven B, Mathenia N et al (2017) Head-drop: a frequent feature of late-onset myasthenia gravis. Muscle Nerve 56:441–444. https://doi.org/10.1002/mus.25526
31. Suiter DM, Leder SB (2008) Clinical utility of the 3-ounce water swallow test. Dysphagia 23:244–250. https://doi.org/10.1007/s00455-007-9127-y