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The Spurious Palsy—Fluctuation of Ocular Myasthenia Gravis Symptoms Characterized by Orthoptics

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Background: Although fluctuating muscular weakness is the hallmark of myasthenia gravis (MG), research into it, especially during the course of the day, remains limited. Understanding the dynamics of myasthenic symptoms is essential for diagnosis and anticipatory treatment. Therefore, in this study, we used orthoptic and other established quantitative and subjective methods to measure ocular myasthenia gravis (OMG) symptoms throughout the day, during the course of 2 months, and in response to treatment.
Methods: The goal of the study was to determine the change of gaze deviation and ptosis during the course of the day, over 2 months, and 1 hour after pyridostigmine intake. Each subject participated in 3 sessions during the day, 2 follow-up sessions, and 1 measurement before and after pyridostigmine. Measurements included the Quantitative Myasthenia Gravis (QMG) score, palpebral fissure height (PFH) photography, the conventional Hess screen test, and a video Hess screen test using video-oculography. The Myasthenia Gravis Activities of Daily Living score (MG-ADL) was obtained on each assessment day. Sum scores were calculated for the gaze deviations of the inner and outer fields of the conventional and the video Hess screen tests.
Results: Twelve patients were recruited, including 11 patients with ocular and 1 patient with generalized MG (mean age 65.7 years, SD 16.9 years; 11 males). The mean sum scores of both the conventional and the video Hess screen test showed a worsening in the evening, reaching significance in the outer field of the Hess screen test (mean increase 13.4°, SD 15.3°, $P = 0.02$). Similarly, ptosis also worsened during the day, with a significant decrease in PFH in the evening (mean decrease 0.53 mm, SD 0.55 mm, $P = 0.04$). Although ptosis improved significantly after pyridostigmine intake (mean increase 0.96 mm, SD 1.05, $P = 0.03$), no significant changes were observed in the sum deviations of the Hess screen tests ($P = 0.6$). Both ptosis and the sum scores generally improved over the 2-month period, even in some patients without any therapeutic adjustments. Correspondingly, the mean QMG and MG-ADL scores decreased.
Conclusions: This prospective cohort study provides insight into the dynamics of OMG, which is crucial for the optimization of diagnostic and therapeutic approaches. Our orthoptic measurements demonstrated the worsening of OMG symptoms after daily activity and a better response of ptosis to pyridostigmine than diplopia. The complexity of this fluctuating disease leads to strong interindividual variability, which requires an individual approach to improve the quality of life of patients with MG.

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Myasthenia gravis (MG) is an autoimmune disease that affects neuromuscular transmission in striated muscles, causing fatigable and fluctuating muscle weakness. The English physician Thomas Willis,[1] who also coined the term "neurology," described what was probably the first case of MG in 1672 as a "spurious palsy." The case involved a young woman who experienced muscle weakness and difficulty speaking that worsened with physical activity but improved with rest. Although the specific diagnosis was still unknown, fatigability was already recognized as a distinct clinical feature of this disease.

Referred to as "the great masquerader," MG has a broad spectrum of clinical presentations. In approximately 85% of cases, MG initially presents with only ocular symptoms such as ptosis or diplopia. However, progression to generalized myasthenia, including bulbar and peripheral muscle weakness, occurs in 50%–80% of cases, mainly within the first year.[2,3] Diagnosis is challenging, particularly in the case of ocular myasthenia gravis (OMG). This is mainly because of a lower detection rate of seropositive acetylcholine receptor (AChR) antibodies of approximately 50% in OMG compared with approximately 90% in generalized myasthenia gravis, and fluctuating symptoms or confusion with other ophthalmic diseases.[4–6]

In OMG, patients experience diplopia and ptosis because of fatigable weakness of the extraocular muscles

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(EOMs). As the disease progresses, the pattern of involved eye muscles can change frequently, even for a short time period, such as a few weeks. Although it is the hallmark of the disease, research into the fluctuation of the disease's symptoms is still scarce, especially during the course of the day. A thorough understanding of the dynamics of myasthenia gravis is vital for both physicians and patients, because it plays an essential role in the diagnostic process and optimization of treatment strategies.

Therefore, we used orthoptic and other quantitative and subjective methods to measure OMG symptoms throughout the day, during the course of 2 months, and in response to treatment. In a prospective fashion, we recruited a cohort of patients with MG, aiming to better understand the characteristics of this relatively rare disease.

METHODS

Ethics

The study received approval from the Zurich Ethics Committee (BASEC 2019-00240), adhered to the Declaration of Helsinki, and written informed consent was obtained from all participants. The investigational device used in the study was approved by Swissmedic (10000515) and registered in the European database of medical devices (CIV-19-05-028506).

Subjects

Participants were recruited from the Departments of Ophthalmology and Neurology at the University Hospital Zurich between March and August 2023. Inclusion criteria were age 18 years or older, confirmed diagnosis of ocular or generalized MG, no overnight pyridostigmine intake, capability and willingness to participate in the study, and ability to understand the study information and consent form. Exclusion criteria included very poor visual acuity and incapability to follow the study protocol.

Examination Procedure

Before testing, pyridostigmine withdrawal overnight (minimum 10 hours) was required. To ensure reproducibility, all tests were conducted by the same investigator. Mobile equipment was used to examine the patients either at home or as inpatients.

Full-day assessment: The same tests were performed in the morning (8–10 AM), at midday (12–2 PM), and in the afternoon (4–6 PM). One session included the Quantitative Myasthenia Gravis (QMG) score, palpebral fissure photography, a conventional Hess test, and a video Hess test using video-oculography. The Myasthenia Gravis Activities of Daily Living (MG-ADL) was obtained once in the morning.

Follow-up assessments: Two additional midday sessions with the same tests were performed at approximately 1-month intervals.

Postpyridostigmine: After completion of the tests at one of the follow-up visits, patients were administered 60 mg oral pyridostigmine followed by the same tests 1 hour later.

Myasthenia Gravis Activities of Daily Living Scale and Quantitative Myasthenia Gravis Score

On each assessment day, disease severity was classified with the MG-ADL, and during each session, the QMG score was obtained as a quantitative clinical reference.[7,8] Vital capacity was assessed using the EasyOne Air spirometer (ndd Medizintechnik, Zurich, Switzerland). Grip strength was measured with the Jamar Plus+ Hand Dynamometer (Sammons Preston, Bolingbrook, IL).

Hess Screen Test

A standardized Hess screen test was performed, where the patient was seated in front of a gray screen featuring a red grid.[9] The head was stabilized with a chin rest positioned 50 cm from the screen. While looking through red-green glasses, the patient was instructed to point a red laser pointer at 17 targets on the grid, including a center target at 0°, 8 targets on the inner field at 15°, and 8 targets on the outer field at 30° eccentricity. Because this method breaks binocular fusion, the distance between target and laser light is equivalent to the patient's phoria.[9] The test was repeated for the other eye by switching the glasses. The paper charts were scanned, and the coordinates were analyzed using MATLAB software (MATLAB R2022b, The MathWorks Inc, Natick, MA).

Palpebral Fissure Height

A picture was taken with a smartphone on a tripod (iPhone XR, Apple Inc. Cupertino, CA), and flash was used to determine the pupils by its reflection. Palpebral fissure height (PFH) was measured on the picture from the lower to the upper eyelid margin through the center of the pupil, using a ruler on a headband as reference.

Video-oculography

A research prototype of binocular video goggles (Natus Medical Inc., Middleton, WI) was used to measure strabismus angles. A head-fixed laser projected the targets of the 0 ± 15° inner field of a Hess grid onto the wall. During recording, the eyes were alternately covered with LCD shutters. For each fixation point, 3 cycles were performed, with each eye blocked for 2 seconds.[10]

Analysis of Results

For each target point, the horizontal and vertical deviations were determined for both eyes, and the direct distances between the gaze positions of the right and left eyes were calculated using the Pythagorean formula and summed into sum scores to give the total deviation of the inner and outer fields. Statistical analysis was done using paired *t* tests to compare 2 related sets of outcome values.

RESULTS

Patient Characteristics

Twelve patients from our neuro-ophthalmology clinic were enrolled, with a mean age of 65.7 ± 16.9 (SD) years: 11 with ocular and 1 with generalized MG. The diagnosis was made through a comprehensive diagnostic work-up, including a standard radioimmunoassay (RiaRSR AChRAb kit from RSR Ltd, Cardiff, United Kingdom) and an edrophonium test in 4 patients. Ten (83%) patients were seropositive for AChR antibodies and 2 (17%) for anti-Titin antibodies. The 2 seronegative patients were diagnosed by the edrophonium test. Seven patients were recently diagnosed, while 5 patients were diagnosed more than 1 year before enrollment. All but 1 patient were men. Six individuals reported daily diplopia, 4 occasional diplopia, and 4 had daily ptosis. At enrollment, all patients were already receiving pyridostigmine treatment, 4 also received prednisone, and 2 received immunosuppressants (azathioprine, secukinumab for psoriatic arthritis). Two patients underwent thymectomy, one of them during study enrollment, having a thymoma. Baseline demographic and clinical characteristics are shown in **Supplemental Digital Content 1** (see Table 1, http://links.lww.com/WNO/A921).

Each participant underwent 1 full day, 2 follow-up, and 1 pre- and postpyridostigmine assessment, totaling 72 recording sessions. All 12 patients were included in the Hess test analysis, because all had either diplopia or Hess test results incompatible with simple heterophoria. For PFH analysis, only 7 patients with visible ptosis were included, 2 with bilateral ptosis.

Full-Day Assessments

Figure 1 shows the PFH and Hess test results of a typical patient with left-sided ptosis and diplopia, measured in the morning (Fig. 1A, B), midday (Fig. 1C, D), and evening (Fig. 1E, F) of the same day. Throughout the day, the Hess test sum scores (total deviation of the inner and outer fields) increased, while PFH decreased, indicating worsening ptosis. Figure 2A shows the sum scores of all participants for the conventional Hess test (inner and outer fields) and the Hess test recorded with video goggles. The video Hess test results were comparable with the inner field of the conventional Hess test. All 3 mean sum scores increased notably in the evening compared with the morning, reaching significance in the outer field of the conventional Hess test (mean increase 13.4 ± 15.3° [SD], $P = 0.02$). Figure 2B illustrates the PFH changes during the day, with a significant decrease in the evening (mean decrease 0.53 mm ± 0.55 mm [SD], $P = 0.04$). The QMG (not shown), also obtained 3 times daily, showed a nonsignificant increase toward the evening (5.58–5.75 out of 39, $P = 0.7$). One patient with bilateral ptosis and diplopia (Fig. 2A, B dashed black line) was excluded from the mean calculation because of hospitalization and sleep between measurements. This unintentional "sleep test" resulted in improvement of his ptosis during the day (Fig. 2C).

Pre- and Postpyridostigmine

Figure 3 illustrates PFH and Hess test results before and 1 hour after oral administration of 60 mg pyridostigmine in an OMG patient with left-sided ptosis and diplopia. Although ptosis improved notably from a PFH of 8.4–11.0 mm, Hess test sum deviations decreased only slightly. The same trend was seen in the combined results of all patients included (Fig. 4). The PFH increase after pyridostigmine (Fig. 4A) was significant (mean increase 0.96 mm ± 1.05 mm [SD], 1 [11%] without change, 1 [11%] decrease, 7 [78%] increases, $P = 0.03$), whereas no significant change in the Hess test sum deviations (−1.5 ± 9.3° [SD], $P = 0.6$, outer field) was observed (Fig. 4B). Although the mean QMG (not shown) decreased from 5.25 to 4.67, it was not significant ($P = 0.2$).

Follow-up Assessments

Figure 5 shows the PFH and Hess test results of a newly diagnosed OMG patient with left-sided ptosis and diplopia measured for a two-month period, while simultaneously initiating steroid therapy on Day 11 and thymectomy on Day 39 of consecutive measurements. Measurements were made on Day 1 (Fig. 5A, B), Day 29 (Fig. 5C, D), and Day 60 (Fig. 5E, F). Both ptosis and diplopia improved over the 2 months, with ptosis responding more rapidly. A clear improvement in diplopia was noted only after starting steroid therapy. Palpebral fissure height and sum deviations of all included patients generally improved over the 2-month period (see **Figure 6**, **Supplemental Digital Content 2**, http://links.lww.com/WNO/A920). Three patients started steroid therapy between measurements. The mean QMG decreased from 5.75 to 5.00 and the mean MG-ADL from 3.75 to 2.08 out of 24 (not shown).

DISCUSSION

This prospective study provides insight into the fluctuations in OMG, showing a general worsening of OMG symptoms with daily activity and a better response of ptosis than diplopia to pyridostigmine.

The worsening of both ptosis and diplopia during the day corresponds well to muscle fatigability, showing that it occurs not only immediately after exercise but also with normal daily activity. Significance was achieved in PFH and only in the outer field of the conventional Hess screen test. This is not surprising, because with increasing gaze eccentricity, the deviation in the direction of the affected muscle increases.[9] However, the total deviation resulting from underaction of the affected muscle and compensatory overaction of the respective contralateral agonist may be underestimated because of the bilateral condition. It is

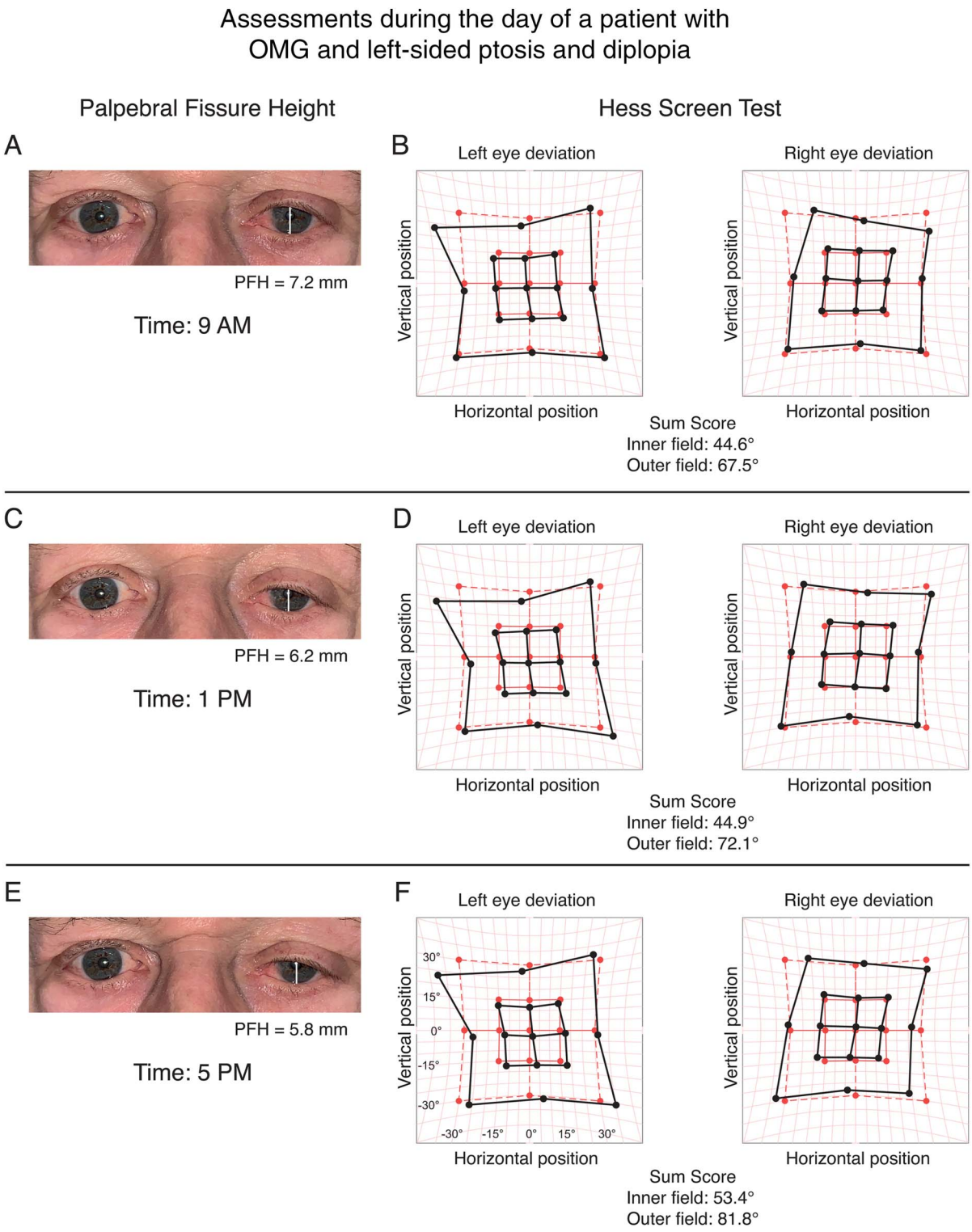

FIG. 1. Palpebral fissure height (PFH) and conventional Hess screen test, measured at 9 AM (**A**, **B**), 1 PM (**C**, **D**), and 5 PM (**E**, **F**) in an ocular myasthenia gravis (OMG) patient with left-sided ptosis and diplopia. There is a decrease in PFH (**A**, **C**, **E**) and an increase in the sum deviations of the inner and outer fields of the Hess screen test (**B**, **D**, **F**) during the course of the day.

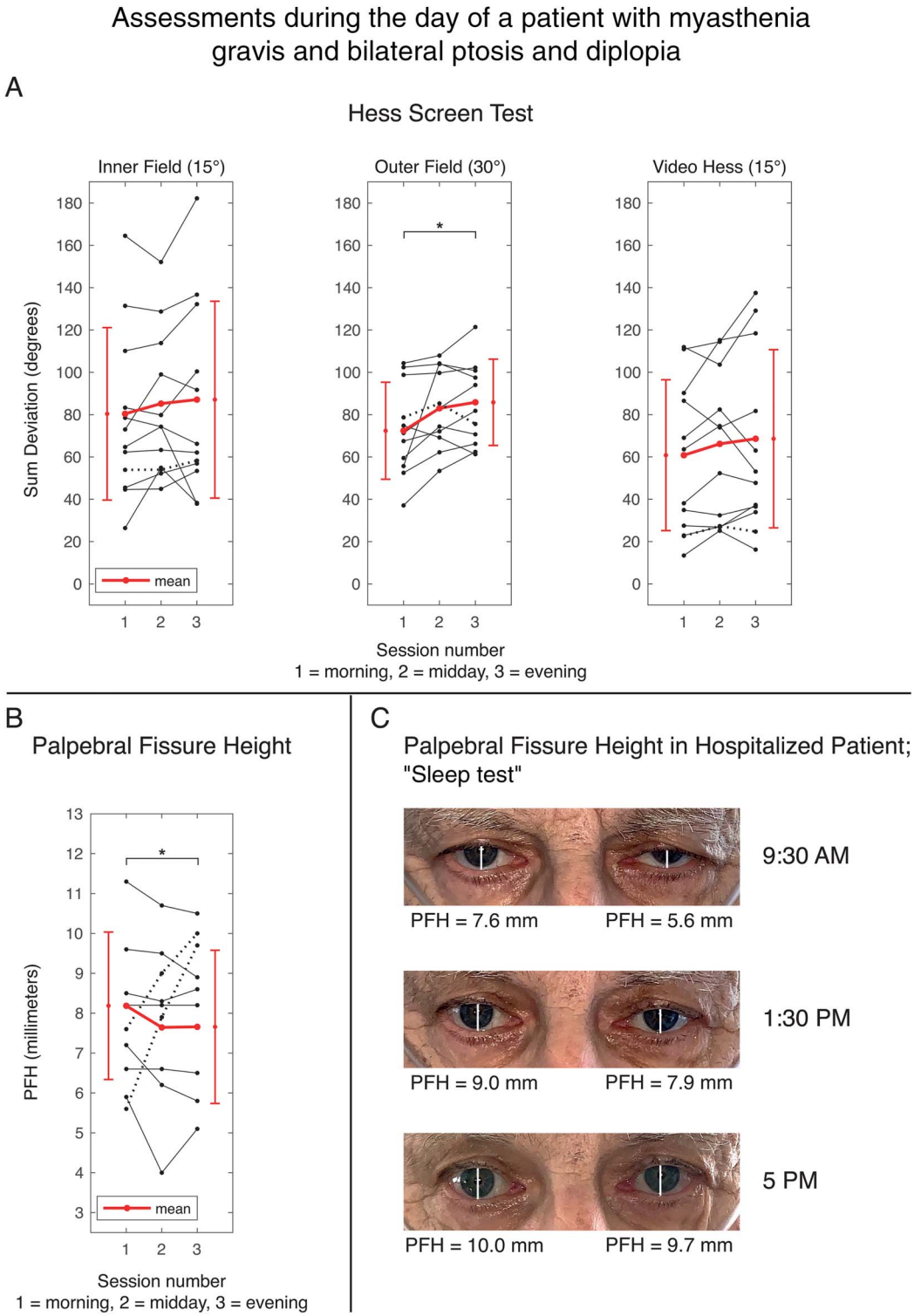

FIG. 2. A. Deviations of the conventional Hess screen test (inner and outer fields) and the video Hess screen test of all included subjects during the day. The mean sum deviations (red) increase during the course of the day, with the results of the outer field being significant ($*P < 0.05$). One patient's outer field data are missing because his deviation was outside the range of the Hess screen. **B**. Palpebral fissure height (PFH) during the day of 7 patients with clinically visible ptosis, 2 of them with bilateral ptosis. The mean PFH (red) significantly decreases ($*P < 0.05$) during the day. One patient was hospitalized (dashed black line) and not included in the mean PFH. **C**. Palpebral fissure height of the hospitalized patient at 9:30 AM, 1:30 PM, and 5 PM. The patient was sleeping during the day and had to be awakened for the midday and evening sessions, unintentionally creating a "sleep test" scenario, resulting in an increase in PFH during the course of the day.

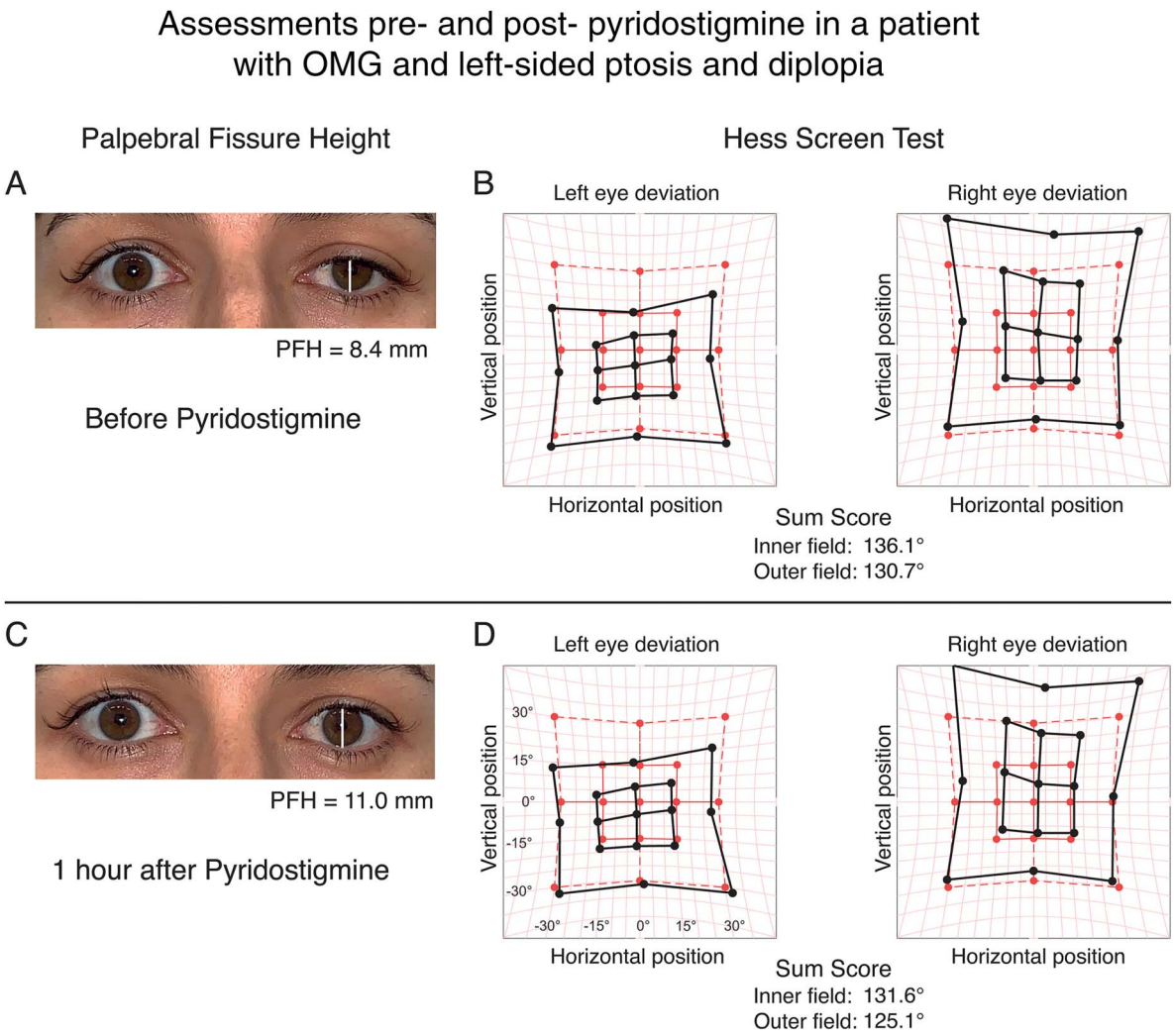

FIG. 3. Palpebral fissure height (PFH) and conventional Hess screen test, measured before (**A**, **B**) and 1 hour after the oral administration of 60 mg of pyridostigmine (**C**, **D**) in an ocular myasthenia gravis (OMG) patient with left-sided ptosis and diplopia. The first measurement was done at 1 PM after a 14-hour withdrawal of pyridostigmine. The patient was not treated with steroids at that time. There is an increase in PFH (**A**, **C**) and a slight decrease in the sum deviations of the inner and outer fields of the Hess screen test (**B**, **D**) after the application of pyridostigmine compared with the measurements before.

interesting to note that the 1 patient who was hospitalized showed decreasing symptoms during the day. Because he mostly slept during the day and just before the tests, he unintentionally provided us with a "sleep test," demonstrating improvement after rest.[11] Consequently, the inter-individual differences were considerable, because many factors can contribute to clinical presentation, such as daytime activity level, corticosteroid and other treatments, and additional factors.

Regarding treatment, we observed pyridostigmine being more effective in improving ptosis than diplopia. Although PFH improved significantly (P = 0.03) after pyridostigmine intake, no significant change was observed in the Hess test (P = 0.6, outer field). This is consistent with previous observations and may be explained by the different fiber types in the EOMs and levator muscle, which may respond differently to pyridostigmine.[12] Because prednisone has been shown to be beneficial in controlling diplopia, corticosteroid therapy is commonly necessary for patients with OMG.[13]

Both ptosis and diplopia improved during the 2-month period, consistent with decreases in QMG and MG-ADL. Because most patients received additional treatment as part of their clinical care, including prednisone and immunosuppressants, this certainly played an essential role in symptom improvement. Interestingly, this trend was observed not only in patients recently started on steroid therapy, but also in patients with no change in treatment. Most of our patients were recently diagnosed, meaning they were probably in an early and less controlled stage of the disease. Therefore, the improvement in these patients could be explained by "regression toward the mean," which refers to the tendency to recruit patients with more severe symptoms who

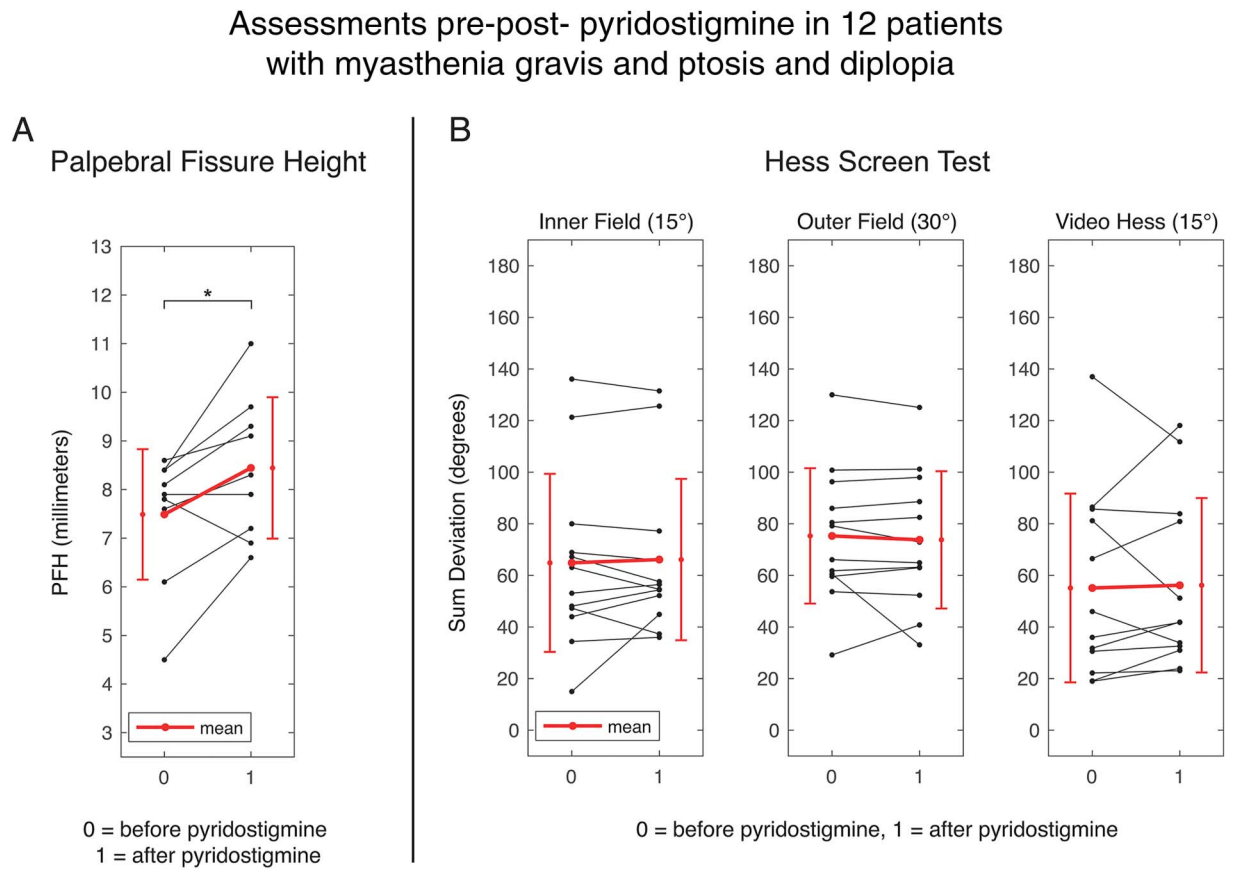

FIG. 4. Palpebral fissure heights (PFH) (**A**) and sum deviations (**B**) of the inner and outer fields of the conventional and of the video Hess screen test before and 1 hour after the oral administration of 60 mg pyridostigmine. The mean PFH shows a significant increase (*$P < 0.05$) after pyridostigmine intake, whereas the mean sum deviation scores do not show any distinct changes.

improve during the study period, even without specific interventions.[14]

As expected, the video Hess test provided results comparable to those of the conventional Hess test. Although limited to a testing field of 15° eccentricity, it is sensitive enough to detect even small shifts because of its mode of action as an automated alternative cover test. In addition to its ability to measure patients with visual suppression, this makes it a valuable method for assessing ocular deviation in patients with MG.[10]

Current diagnostic strategies allow diagnosis of only approximately 60% of MG cases during the first year of the disease.[15] This highlights the need for new diagnostic approaches including the discovery of new antibodies or new electrophysical approaches, such as repetitive ocular vestibular evoked myogenic potentials (roVEMP).[4,16–18] Incorporating orthoptic measurements of diplopia fluctuation into the diagnostic process may help to distinguish OMG from other ocular motility disorders and may be useful to determine the severity of involvement of individual EOMs.[19] As a static test, however, the Hess test does not account for muscle fatigability, which can only be assessed by analyzing changes in the deviation pattern of repeated measurements over time. Keene et al.[19] demonstrated that adding 1 minute of sustained gaze per target during the Hess test can result in a drift phenomenon that represents EOM fatigability in patients with MG. To improve this assessment method, it may be beneficial to measure the drift with video-oculography.

This study is limited by the small number of subjects and the variability in their baseline characteristics and treatment status. Because all subjects were receiving pyridostigmine treatment on enrollment, they can be considered pyridostigmine responders. This sample bias could have positively influenced the pre- and postpyridostigmine assessment results. Because we focused on exploring the qualitative aspects of the dynamics of OMG, we primarily included patients who were either recently diagnosed or in an active stage of the disease. It is worth noting that all but 1 of the enrolled patients were men, which does not reflect the typical sex distribution of OMG, where only 55% are men.[2] Given the mean age of 65.7 years in our study and the bimodal age distribution of MG, with a late-onset peak in men approximately 65 years of age, the male preponderance may not be as surprising,[20] but it certainly limits its applicability to the general population.

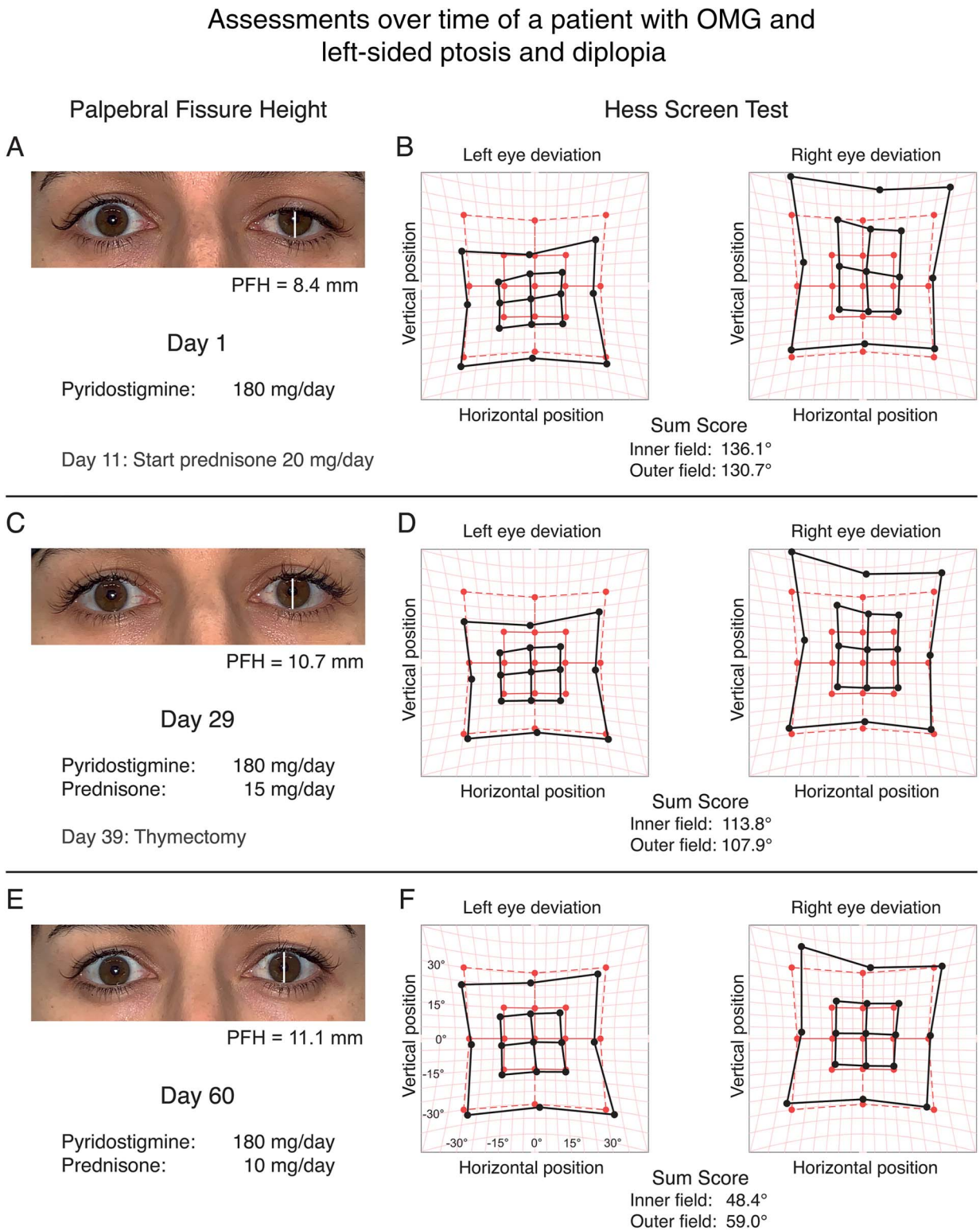

FIG. 5. Palpebral fissure height (PFH) and conventional Hess screen test, measured on the first day of the sequential measurements (**A**, **B**, Day 1), after 1 month (**C**, **D**, Day 29), and after 2 months (**E**, **F**, Day 60) in the same patient as shown in Figure 3. All measurements were taken around noon (12:30 to 2 PM). Treatment with prednisone 20 mg/day was started on Day 11 and gradually reduced to 10 mg/day during the course of the 2 months. There is an increase in PFH (**A**, **C**, **E**) and a decrease in the sum deviation score of the inner and outer fields of the Hess screen test (**B**, **D**, **F**) during the course of the 2 months.

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