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Diagnosing myasthenia gravis using orthoptic measurements: assessing extraocular muscle fatiguability

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ABSTRACT

Introduction Diagnosing ocular myasthenia gravis (MG) can be challenging because serum antibodies are often not detected. We aimed to explore whether determining extraocular muscle (EOM) weakness using orthoptic measures, including an adapted Hess chart examination, can aid in diagnosing MG.

Methods We conducted a prospective study among patients with acetylcholine receptor antibody positive MG (20 recently diagnosed, 19 chronic) and 14 seronegative MG patients. We compared orthoptic measures to 19 healthy and 18 disease controls with Graves orbitopathy, chronic progressive external ophthalmoplegia or oculopharyngeal muscular dystrophy. Maximal eye duction angles were measured using a synoptophore. Gaze deviations between eyes were measured using standard Hess chart examination with addition of 1 min persistent gaze to assess MG-associated fatiguability. Receiver operating characteristics curve analysis was performed.

Results For duction angles, the area under the curve (AUC) was 0.73 comparing MG to healthy, and 0.69 comparing to patient controls. For the outer field of the Hess chart, the AUC was 0.89 comparing to healthy and 0.54 to patient controls. For drift, the AUC was 0.93 comparing to healthy and 0.93 to patient controls. The sensitivity and specificity of the presence of drift was 81% and 100%.

Discussion Orthoptic measurements can be used to diagnose MG by quantifying EOM weakness and fatiguability. Drift during persistent gaze on a Hess chart is specific for MG and could be used for diagnostic purposes. The Hess chart examination is widely available, inexpensive and fast. Moreover, orthoptic measurements may be a clinically relevant outcome measure for clinical trials.

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disease with autoantibodies targeting proteins at the neuromuscular junction, including the acetylcholine receptor (AChR).^{1,2} Fatigable and fluctuating muscle weakness is the hallmark of MG.³ In 85% of MG patients, the first symptoms are ocular, and consist of diplopia and ptosis. A total of 10%–15% of MG patients have only ocular symptoms.⁴ In 50% of ocular patients no detectable antibodies are found

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Diagnosing ocular myasthenia gravis can be challenging because serum antibodies are often not detected, therefore there is a need for more accurate, non-invasive diagnostics. Orthoptic tests, routinely performed tests in for example strabismus correction surgery, can quantify deviation between eyes and movement limitations of the eyes but do not take fatiguability into account.

WHAT THIS STUDY ADDS

⇒ We explored whether determining extra ocular muscle weakness using orthoptic measures, including an adapted Hess chart examination, can aid in diagnosing myasthenia gravis. We found that these orthoptic measurements are valuable in identifying extra-ocular muscle fatiguability, as drift during 1 min persistent gaze on the Hess chart was only present in myasthenia gravis patients.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Measuring persistent gaze using a Hess chart holds promise as a highly specific, non-invasive and easy to perform diagnostic test for myasthenia gravis. In addition, orthoptic measurements can be used to identify the severity of ocular involvement, which may be a promising and clinically relevant outcome measure for clinical trials in ocular myasthenia gravis.

in serum.⁵ In this subgroup, labelled seronegative MG (SNMG), diagnosis is challenging.² Distinguishing ocular MG from mimics, such as Graves orbitopathy (GO), chronic progressive external ophthalmoplegia (CPEO) and ocular pharyngeal muscular dystrophy (OPMD) can be challenging given the similarity in ocular symptoms⁶ and the inaccessibility of extraocular muscles (EOM)s for needle EMG. Therefore, there is a need for accurate, non-invasive diagnostics for ocular SNMG.⁷

Three pairs of EOMs move the eye in all directions: horizontally (medial rectus (MR) and lateral rectus (LR)), vertically when the eye is in abduction (superior rectus (SR), inferior rectus (IR)) and

vertically in adduction (superior oblique (SO) and inferior oblique (IO)). The oblique muscles are also responsible for torsional movement of the eye with contraction of the SO, causing incyclotorsion and the IO, causing excyclotorsion. In MG, diplopia is caused by fatigable weakness of these EOMs. This fatiguability of the EOMs has been studied qualitatively in previous work by using patient reported diplopia during persistent gaze.⁸ In addition, testing fatiguability in sustaining gaze at the bedside is part of the standard examination procedure in ocular MG, with the advantage that the levator palpebrae superioris can also be tested by assessing ptosis during sustained up gaze.⁹ Using orthoptic tests, the absolute movement limitation of each eye can be quantified with the synoptophore and deviations between two eyes with the Hess chart. In ophthalmology, these quantitative orthoptic measurements are routinely performed, for example, during planning of strabismus correction surgery.^{10–12}

Orthoptic measures have been tested before as an additional diagnostic tool in a small group of ocular MG patients by adding the Hess chart as an objective measure before and after the edrophonium test.¹³ However, the standard Hess chart does not take muscle fatiguability into account and evaluating the diagnostic value of orthoptic measures in a well-defined cohort of MG patients could be of interest. Therefore, we aimed to explore whether orthoptic measurements can aid in diagnosis, and whether adding 1 min of persistent gaze to the Hess chart makes it possible to detect MG-related fatiguability.

METHODS

Participants

We included a convenience sample of MG, GO, CPEO and OPMD patients from the Neurology Department and the Ophthalmology Department of the Leiden University Medical Center, Radboud University and the Rotterdam Eye Hospital. Healthy controls were recruited using posters and by asking relatives of the included MG patients.

MG patients were divided in three groups: chronic, recently diagnosed and seronegative. The diagnosis of AChR MG was based on clinically confirmed fluctuating muscle weakness in combination with the presence of serum autoantibodies to AChR in the chronic and recently diagnosed MG patient groups. SNMG was defined as clinically confirmed fluctuating muscle weakness in combination with abnormal decrement during RNS, increased jitter during single fibre EMG testing or a positive response to an acetylcholinesterase inhibitor without the presence of AChR or muscle-specific kinase serum autoantibodies.⁷ Recently diagnosed MG patients fulfilled two criteria: (1) The diagnosis was established less than a year ago and (2) They had never been treated with immunosuppressants; Chronic MG was defined as all patients who received the diagnosis more than a year ago. In the SNMG group no selection was made for disease duration or immunosuppressant status. We also included three disease mimic groups: GO, CPEO and OPMD, and a group of healthy age-matched and sex-matched controls. The diagnosis of GO was defined as the presence of TSH-receptor serum autoantibodies with the presence of ocular symptoms.¹⁴ The diagnosis of CPEO was confirmed with a limb muscle biopsy in all patients¹⁵ and the diagnosis of OPMD was confirmed with molecular genetic testing of the PABPN1 gene.¹⁶ Healthy controls with a history of strabismus were excluded, as were patients with simultaneous diagnosis of MG and GO.

For the MG patients a quantitative MG (QMG) score^{17 18} and a MG activities of daily living (MG-ADL) scale¹⁹ were recorded.

Measuring duction angles using the synoptophore

Duction angles were defined as the range of motion of the eye in degrees in all directions. In this study, unilateral duction angles in all eight cardinal positions of gaze were determined under standardised conditions using the synoptophore (Clement Clarke International, 2002, Edinburgh way, Harlow, Essex, CM20 2TT, England) (figure 1A).²⁰ The patient was instructed to follow a fixation target in all directions. The arm of the synoptophore was moved from 0° towards the final position of gaze, while the patient maintained fixation. When it became apparent for the single observer that the eyes had stopped following the fixation target, a duction measurement was recorded in degrees. Vertical duction angles were measured up to $\pm 30^\circ$ during elevation and depression and horizontal duction angles were measured during adduction and abduction up to $\pm 40^\circ$. The vertical ductions in the four corners were measured in either 25° adduction or abduction.

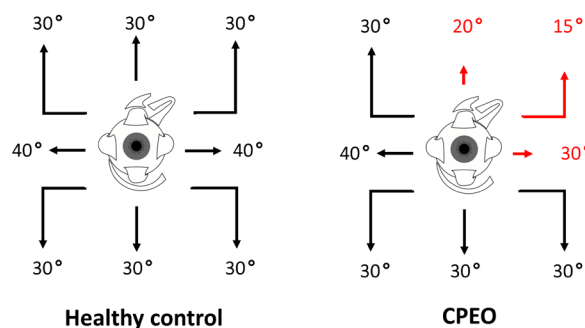
Hess chart

The Hess chart is a routinely used test in for example the planning of corrective strabismus surgery. The aim of the Hess chart is to determine the deviation between two eyes when fixing on one point by using the difference in foveal projection of the eyes.¹⁰ Cyclotorsion of the eyes cannot be measured with the Hess chart. In this study, the eyes were tested sequentially, starting with the left eye. The patient wore glasses with a green filter in front of the tested eye and a red filter in front of the reference eye. The patient was instructed to place a green light from a laser pointer (only visible to the tested eye) for each of the points on the red light (only visible to the reference eye) as illuminated on the Hess screen by the observer (Clement Clarke International, V6908000, Edinburgh way, Harlow, Essex, CM20 2TT, England). The location of the green light from the laser was manually annotated by a single examiner on a Hess chart. This location was estimated with a precision of a single degree using the 5° grid lines on the chart.²¹ The central point and all eight inner field points were measured first in a consistent order (vertical order: central, top and bottom, horizontal order per vertical line: middle, left and right). Subsequently, the outer field points were all measured in the same order and the conventional Hess chart examination was extended with 1 min of persistent gaze to determine fatiguability for these outer field points in the same run. The first positions after fixation and the maximal deviations during this 1 min period were charted by the researcher (figure 1B). When a patient was unable to maintain 1 min of persistent gaze, the maximum deviation was noted. When the green light was out of scope of the Hess screen (ie, on the wall behind the screen) a measurement was considered out of range. No other orthoptic eye movement examinations were performed in this patient cohort.

Translating the Hess chart measures to weakness of individual EOM

In general, deviations on the Hess chart cannot be directly linked to an individual EOM, as the movement of both eyes are correlated and therefore underaction in one direction could be caused by overaction of the antagonising EOM of the other eye. However, considering that the disease mechanism is muscle weakness in MG, CPEO and OPMD, it is very unlikely that the affected EOM itself gives rise to an overaction on the Hess chart in its own direction. As a result, in these patients underacting directions can be directly linked to the weakness of an individual EOM (figure 2) and overactions,

A. Measuring duction using the synoptophore



B. Measuring deviations on the Hess chart

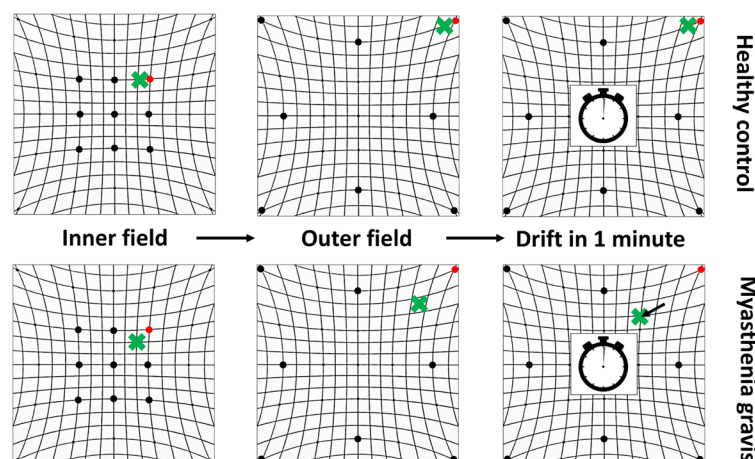


Figure 1 (A) In all eight cardinal positions of gaze, unilateral duction angles were measured using the synoptophore, as depicted in the photograph on the left. An example of a healthy participant with no duction limitations is shown in the middle. On the right, a CPEO patient with limited ductions in elevation and adduction. (B). On the left a photograph of the Hess screen test is shown. The patient wears red-green glasses and is asked to point at the red light with a green laser pen. The deviations in the inner field, the outer field and after 1 min of persistent gaze are charted by the researcher. Typical example of a measurement from a healthy control and an MG patient are shown. CPEO, chronic progressive external ophthalmoplegia; MG, myasthenia gravis.

including out of range measurements, can be excluded as these are the result of an underacting muscle of the contralateral eye. For GO, this interpretation cannot be made, as overactions are often the result of swelling and stiffening of the EOM.^{22 23} Therefore, the translation to the involvement pattern of individual EOM was not made for GO patients.

Sum scores for the duction angle limitations and the Hess chart deviations

To quantify the total muscle weakness for the inner field, the outer field and drift, the degrees of deviation for all six muscles were summated to calculate sum scores.²⁴ A sum score of more than 6° for the outer field was considered to be clinically relevant, as this was the average of the healthy controls plus 2 SD.

Statistical analysis

Hess chart deviations, duction angles as measured with the synoptophore and continuous baseline characteristics were compared between all groups using one-way analysis of variance with Dunnett's multiple comparisons test for post hoc comparisons. Post hoc comparison was performed with healthy controls as a reference group. Categorical baseline characteristics were compared using Pearson's χ^2 test.

To determine the diagnostic yield of the duction angles as measured with the synoptophore, and the inner field, outer field and drift as measured with the Hess chart, we created receiver operating characteristics (ROC) curves and reported the area under the curve (AUC) with 95% CI and p values. All data are presented as number of patients (percent) for categorical variables and as mean $\pm$ SD for continuous variables. Statistical analysis was performed with SPSS V.23 (IBM) and p values below 0.05 were considered significant.

Data availability

Anonymised data presented in this article will be made available at the request of a qualified investigator. Requests should be made to M.R. Tannemaat (m.r.tannemaat@lumc.nl). Raw Hess charts and spider plots depicting the affected EOM per individual participant have been added as online supplemental data.

RESULTS

Participant characteristics

We included 16 healthy controls, 20 recently diagnosed MG patients, 19 chronic MG patients, 14 SNMG patients, 6 CPEO patients, 6 OPMD patients and 6 GO patients. Demographic and clinical baseline characteristics of all participants

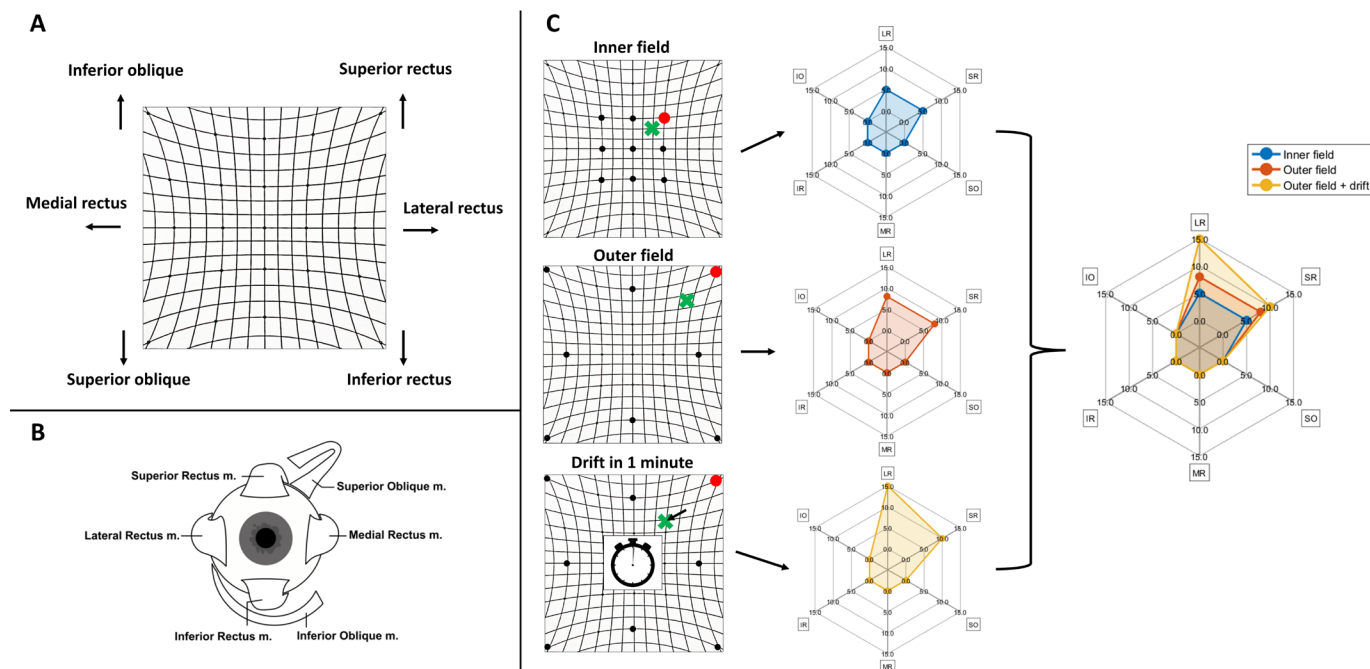


Figure 2 (A) The under-action on the Hess chart was attributed to weakness of the individual EOM by using the directions shown next to the chart. (B). Anatomical representation of the right eye with the four recti eye muscles and the two oblique eye muscles. (C). The deviations in degrees for the individual EOM were plotted in a spider plot for the inner field, the outer field and drift during 1 min of persistent gaze in the outer field. EOM, extra ocular muscle.

are shown in [table 1](#). No significant differences were found between sex and age between all groups. No significant differences were found between MG phenotype (ocular or generalised), MG-ADL and QMG between recently, diagnosed, chronic and SNMG. There was an obvious difference in disease duration between recently diagnosed and chronic MG patients. The ocular MG patients and the generalised MG patients did not significantly differ in age (60.4 ± 10.9 vs 52.2 ± 19.7). Sex was significantly different between

ocular and generalised MG patients (78% male vs 35% male, $p < 0.001$).

Duction angles as measures with the synoptophore

Duction angles, as measured with the synoptophore, are depicted in [figure 3](#) for all eight cardinal directions per eye, with the fraction of patients' eyes per group that did not have any limited ductions in green. None of the healthy

Table 1 Baseline characteristics and sum scores of 87 participants included in this study: 16 healthy controls, 20 recently diagnosed myasthenia gravis (MG) patients, 19 chronic MG patients, 14 seronegative MG (SNMG) patients, 6 chronic progressive external ophthalmoplegia (CPEO) patients, 6 oculopharyngeal muscular dystrophy (OPMD) patients and 6 graves orbitopathy (GO) patients

	MG Recently diagnosed n=20	MG Chronic n=19	MG Seronegative n=14	CPEO n=6	OPMD n=6	GO n=6	Healthy controls n=16	P value
Age (yrs)	59±19	51±16	57±9	49±14	62±10	44±12	54±13	0.243
Sex								0.754
Female	7 (35%)	9 (47%)	7 (50%)	3 (50%)	4 (67%)	4 (67%)	9 (56%)	
Male	13 (65%)	10 (53%)	7 (50%)	3 (50%)	2 (33%)	2 (33%)	7 (44%)	
Phenotype								0.105
Ocular	12 (60%)	6 (32%)	9 (64%)	—	—	—	—	
Generalised	8 (40%)	13 (68%)	5 (36%)	—	—	—	—	
Disease duration (months)	4.0±2.2	75.6±87.9	25.6±60.5*	—	—	22.8±35.9	—	<0.0001
MG-ADL	5.8±3.3	5.5±4.2	5.0±2.7	—	—	—	—	0.791
QMG	9.2±6.0	9.8±7.7	8.3±4.6	—	—	—	—	0.812
Sum scores								
Duction angle limitations	10±15	23±47	22±30	121±61	40±44	7±15	0±0	<0.0001
Inner field deviations	13±12	16±15	15±15	23±25	3±1	17±24	2±3	0.021
Outer field deviations	16±12	11±13	23±19	19±19	11±9	25±20	2±2	<0.0001
Drift in 1 min	13±8	12±7	12±10	0±0	0±0	1±2	0±0	<0.0001

Data are presented as number of patients (%) for categorical variables and as mean±SD for continuous variables.

*Four of the seronegative MG patients had chronic disease with a time since diagnosis of over 1 year.

MG-ADL, MG-activities of daily living; QMG, quantitative myasthenia gravis.

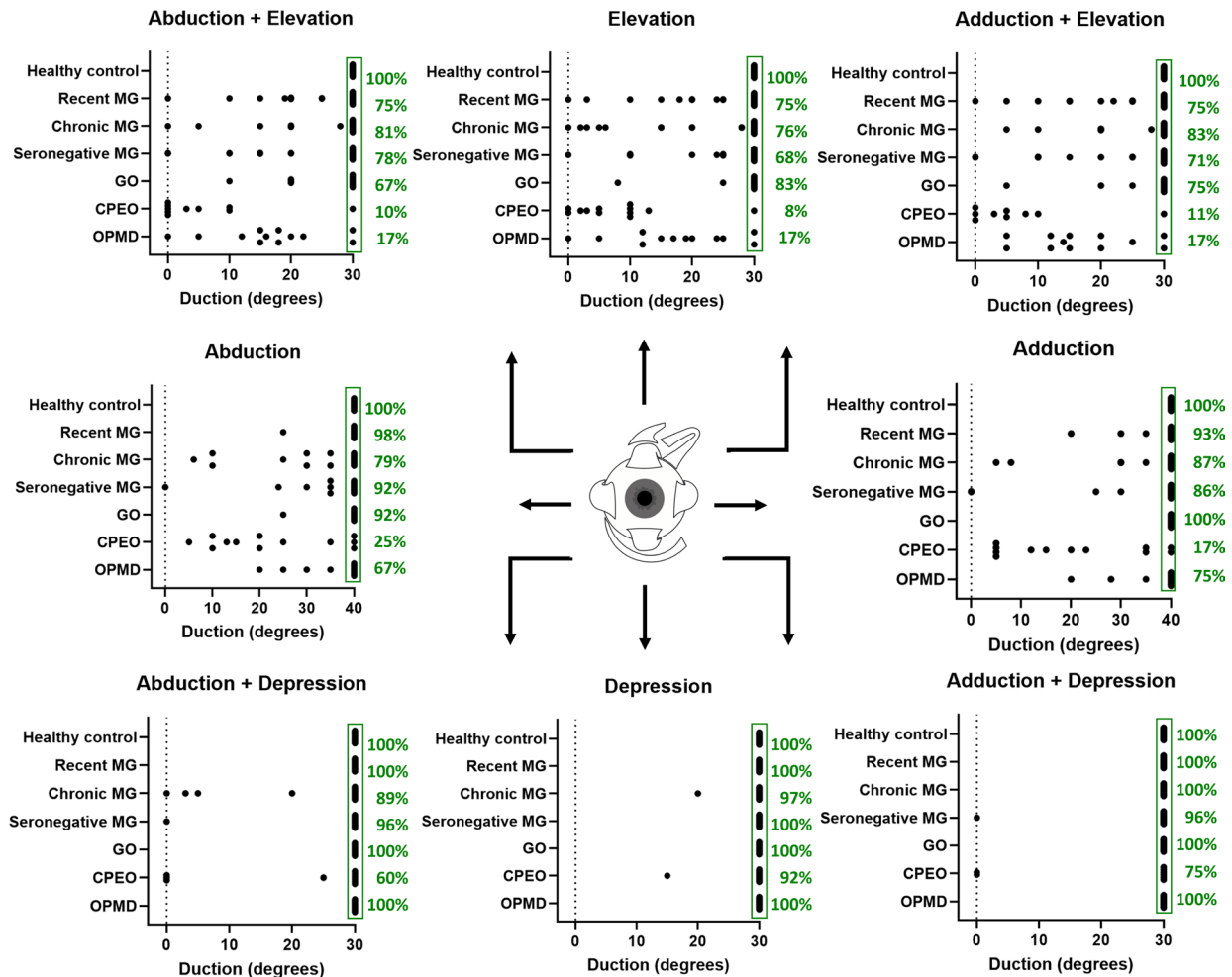


Figure 3 Duction angles as measured with the synoptophore for all eight cardinal directions per eye. In green, the fraction of patients' eyes per group that did not have any limited ductions. Depression limitations are clearly less prevalent than elevation and horizontal limitations for all patient groups. No limited ductions were found in healthy controls. CPEO, chronic progressive external ophthalmoplegia; GO, graves orbitopathy; MG, myasthenia gravis; OPMD, ocular pharyngeal muscular dystrophy.

controls had duction limitations. In the combined MG group, limitations in elevation were most prevalent (36% patients affected of which 58% both eyes were affected, with a mean of 15° limitation), compared with horizontal abduction (19% of patients affected of which 50% both eyes affected, with a mean of 16° limitation) and adduction (19% of patients affected of which 20% both eyes affected, with a mean of 19° limitation). In addition, a limitation in depression was observed in only one MG patient unilaterally (figure 3).

Deviations and drift on Hess chart

Qualitatively, large differences were already apparent in the pattern on the Hess charts between different groups. Hess charts obtained from recently diagnosed MG patients, chronic MG patients, CPEO patients and healthy controls are shown in figure 4 (for the Hess charts of all groups see online supplemental figure 1) and for the Hess charts of individual patients see online supplemental PowerPoint file). All patient groups showed more deviations in both inner and outer fields than healthy controls, especially vertically. An exodeviation below 5° was seen in many healthy controls, which is a known phenomenon with binocular testing, commonly referred to as divergence bias.¹² In addition, drift (as depicted in red in figure 4) was much more prevalent in

the MG groups, compared with both other patient groups and healthy controls.

Sum scores for duction angle limitations, deviations and drift

The sum scores for the duction angle limitations as measured with the synoptophore and the deviations as measured with the Hess chart are depicted in figure 5. Sum scores for duction angle limitations were significantly different (0° for healthy controls, 10° for recent MG, 23° for chronic MG, 22° for SNMG, 7° for GO, 121° for CPEO and 40° for OPMD, $p < 0.0001$); post hoc analysis showed CPEO was different from healthy controls ($p < 0.0001$). For the inner field of the Hess chart, significant differences were found between groups (2° for healthy controls, 13° for recent MG, 16° for chronic MG, 15° for SNMG, 17° for GO, 23° for CPEO and 3° for OPMD, $p = 0.02$), and post hoc analysis showed chronic MG ($p = 0.03$) and CPEO ($p = 0.02$) patients were different from healthy controls. For the outer field, significant differences were found between groups (2° for healthy controls, 16° for recent MG, 11° for chronic MG, 23° for SNMG, 25° for GO, 19° for CPEO and 11° for OPMD, $p < 0.0001$) and post hoc analysis showed recent MG ($p = 0.02$), SNMG ($p = 0.0007$) and GO ($p = 0.004$) were different from healthy controls.

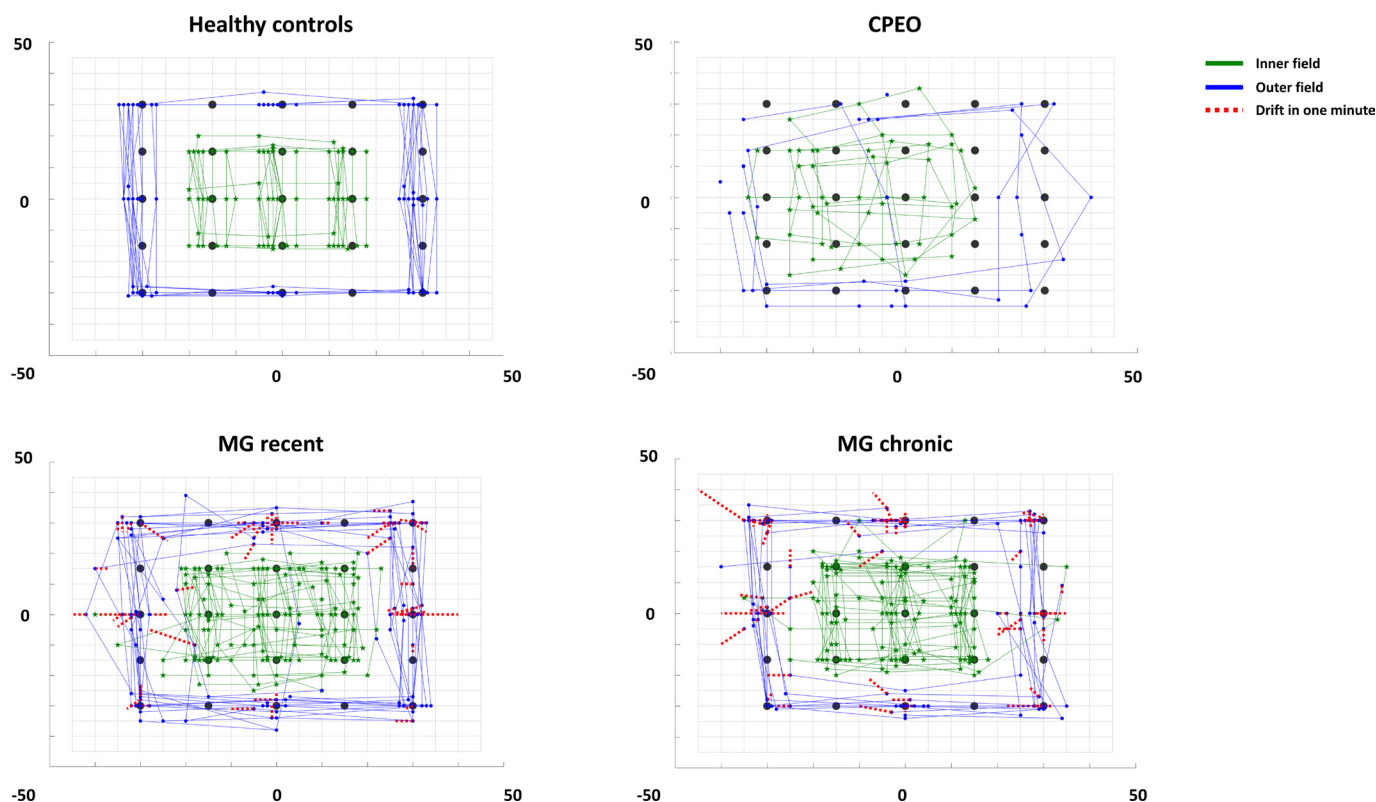


Figure 4 Hess charts corresponding to the left eyes of all healthy controls, CPEO patients, recently diagnosed MG patients and chronic MG patients. Individual patients are superimposed. Measurements of the inner field are green and measurements of the outer field are blue and connected. Drift after 1 min is plotted using red dashed lines. CPEO, chronic progressive external ophthalmoplegia; MG, myasthenia gravis.

Drift sum scores were significantly different between all groups (0° for healthy controls, 13° for recent MG, 12° for chronic MG, 12° for SNMG, 1° for GO, 0° for CPEO and 0° for OPMD, $p < 0.0001$), and post hoc analysis showed that all three MG groups ($p < 0.0001$) were different from healthy controls. The duction angle limitation sum scores were not significantly different between ocular ($9^\circ \pm 22^\circ$) and generalised ($21^\circ \pm 42^\circ$) subgroups of MG. For the Hess chart, comparing ocular and generalised MG, the inner field (19° vs 16°), outer field (20° vs 15°) and drift sum score (14° vs 10°) did also not differ significantly.

Hess deviations in MG patients without duction limitations

Of the 24 MG patients who had limited ductions, the average sum score for the Hess chart inner field and outer field was $21.8^\circ \pm 15.1^\circ$ and $22.4^\circ \pm 17.8^\circ$ respectively. Of the 29 MG patients who did not have any limited duction, the average sum score for the Hess chart inner field and outer field was $8.2^\circ \pm 9.6^\circ$ and $10.3^\circ \pm 9.2^\circ$, respectively. Twelve of these patients (41%) had an outer field sum score above 6° , and therefore, had clinically relevant Hess chart deviations without duction limitations.

Diagnostic value of orthoptic measures

ROC curves were calculated for the duction angles as measured with the synoptophore, and the inner field, outer field and the drift on the Hess chart by comparing the MG patients with healthy controls and with GO, CPEO and OPMD patients combined ('patient controls') and are shown in figure 6. For duction angles, AUC was 0.73 (95% CI 0.61 to 0.85, $p = 0.006$) for MG compared with the healthy controls

and 0.69 (95% CI 0.54 to 0.84, $p = 0.016$) for MG compared with patient controls. For the inner field of the Hess chart, the AUC was 0.81 (95% CI 0.71 to 0.91, $p = 0.0002$) compared with healthy controls and 0.57 (95% CI 0.41 to 0.73, not significant) compared with patient controls. For the outer field, the AUC was 0.89 (95% CI 0.81 to 0.96, $p < 0.0001$) compared with healthy controls and 0.54 (95% CI 0.38 to 0.70, not significant) compared with patient controls. For drift, the AUC was 0.93 (95% CI 0.88 to 0.99, $p < 0.0001$) compared with healthy controls and 0.93 (95% CI 0.87 to 0.99, $p < 0.0001$) compared with patient controls. The AUC was similar for ocular versus generalised MG (both 0.94). The highest diagnostic yield in MG patients compared with the other patient groups was achieved for the drift sum score, with a sensitivity of 81% and specificity of 100%, using a threshold of 6° .

EOM involvement pattern

Horizontal movement and upgaze was most deviant, with at least one LR and an MR deviating more than 5° in 43% and 57% of MG patients, and at least one SR and an IO deviating more than 5° in, respectively, 45% and 40% of MG patients. Downgaze deviated less frequently more than 5° , with an IR and an SO being involved in 28% and 23% of MG patients. Only one healthy control showed a deviation for the MR muscle of 5° or higher.

DISCUSSION

In this work, we studied whether our extended orthoptic tests could aid in the diagnosis of MG. We applied the Hess chart in a novel way, by assessing drift on the Hess chart as a direct

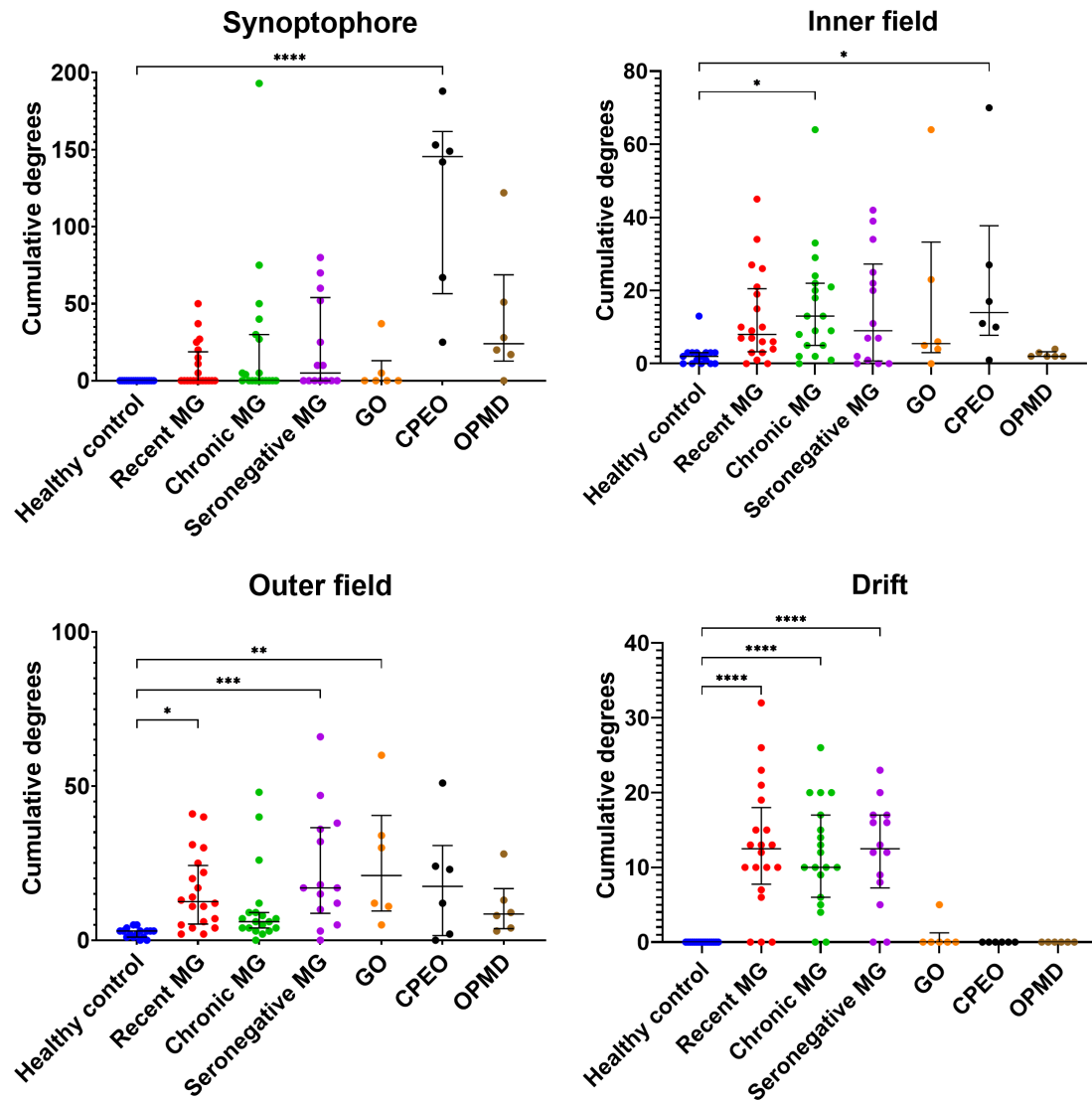


Figure 5 Sum scores for limitations in duction angles of both eyes as measured with the synoptophore, and the relative deviations between eyes on the Hess chart for the inner field, outer field and the drift during 1 min persistent gaze are depicted per group. Significant post hoc group differences are marked with asterisks. Most limited ductions were observed in the CPEO patients, in contrast with the Hess chart deviations given the symmetry of EOM involvement in CPEO. With the exception of one GO patient, the drift phenomenon occurred exclusively in MG patients. CPEO, chronic progressive external ophthalmoplegia; EOM, extra ocular muscle; GO, graves orbitopathy; MG, myasthenia gravis.

measure of EOM fatiguability. The presence of drift during 1 min of persistent gaze had a sensitivity of 81% and a specificity of 100%, compared with our patient control groups. This test could therefore constitute a promising, highly specific diagnostic test for MG, as it is relatively easy to implement in routine clinical testing, affordable and widely available.

Ocular SNMG is challenging to diagnose, resulting in misdiagnoses and treatment delays.⁷ The diagnosis of ocular MG can be made probable by bedside testing for fatiguability and fluctuations in ocular symptoms. These tests include ptosis assessment during persistent up gaze, observations of rapid initial saccades²⁵ or Cogan's twitch, repeated observations to assess fluctuations and an examination before and after the administration of an acetylcholinesterase inhibitor. Additionally, quantitative and objective tests to diagnose ocular MG exist. Currently, these patients are diagnosed with single-fibre electromyography and repetitive nerve stimulation, but both these tests have limitations.² The diagnostic yield of

single-fibre electromyography appears to vary, with sensitivities ranging from 0.62 to 0.99 and specificities ranging from 0.66 to 0.98 in different studies.²⁶ Repetitive nerve stimulation is very specific but not very sensitive in ocular MG.²⁶ Given the anatomical difficulty of electrophysiological testing of the eye muscles directly, more objective measures of EOM fatiguability are lacking.²⁷ Other new diagnostic tests have recently been developed for the diagnosis of ocular MG, such as repetitive ocular vestibular evoked potentials^{28 29} or videonystagmography,³⁰ but these tests require specialised equipment. Our extended orthoptic tests are objective, specific and sensitive to the fatiguability of the EOM in MG, and therefore, constitute an easily implementable diagnostic alternative.

The use of orthoptic tests enabled us to objectively quantify the overall pattern of involved EOMs in our patient groups. Despite fluctuations in weakness and involvement pattern, some EOMs appear to be more frequently involved in MG than others. In previous studies on the involvement pattern of

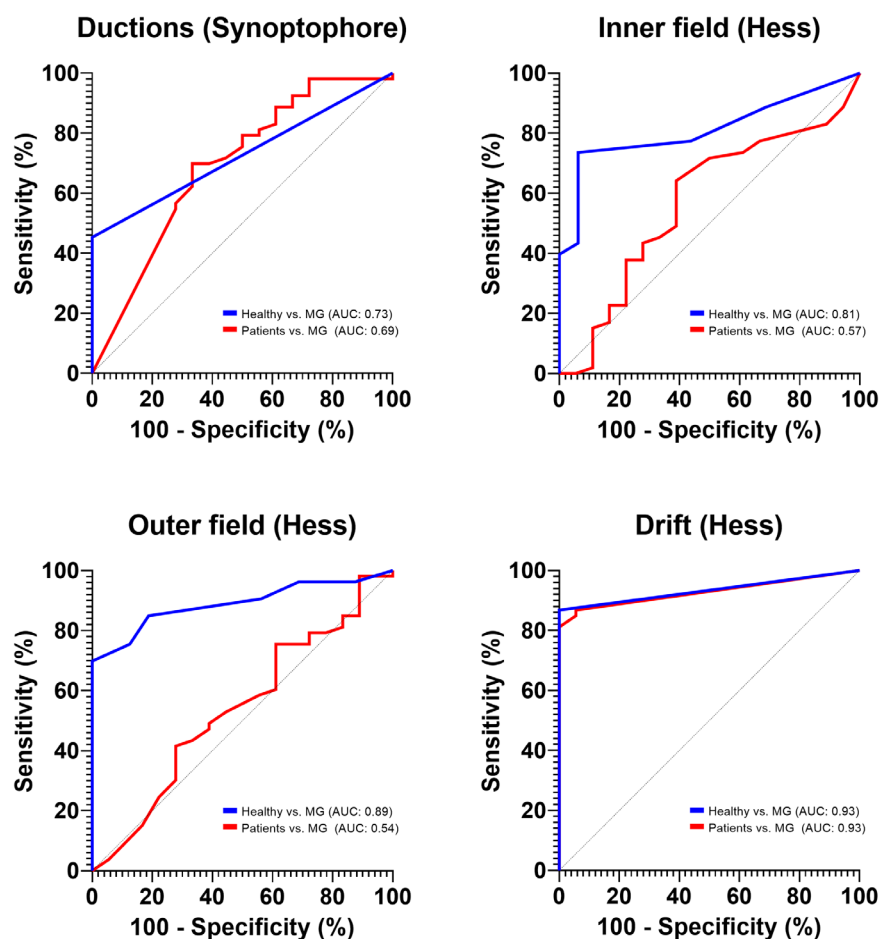


Figure 6 Receiver operating characteristics (ROC) curves for the duction angles as measured with the synoptophore, and the inner field, outer field and the drift on the Hess chart. The ROC curve comparing MG patients and healthy controls is depicted in blue and the ROC curve for MG patients and other patient groups is depicted in red. The AUC of MG versus the other patient groups is highest for the drift on the Hess chart, with a specificity of 100% and a sensitivity of 81% at a sum score threshold of 6°. AUC, area under the curve; MG, myasthenia gravis.

EOM in MG, the SR, the IO and the MR have been reported to be more frequently involved than the IR, SO and the LR, without any consistent pattern.^{8 31–34} We confirm these findings with similar frequencies of involved EOM, although variability between patients remains high. In CPEO and OPMD, the SR appears to be the most predominantly involved muscle, in line with results from previous studies.^{35–37}

Interestingly, a remarkably high percentage (41%) of MG patients without a measurable ophthalmoparesis had Hess chart deviations. The limitations in ductions are measured monocularly using the synoptophore and translate directly to the degree of ophthalmoparesis. This might be partially explained by measurement limitations of the synoptophore, which are 30° vertically and 40° horizontally. The difference between the limitation of the synoptophore and the maximal gaze in healthy volunteers is most pronounced in depression, where volunteers showed an average of 55° maximal gaze.³⁸ We hypothesise that absolute limitations in ductions only occur in cases in which EOM weakness is so severe that movement of the eye is restricted in certain directions. In contrast, Hess chart-derived deviations are based on a relative mismatch in gazing direction between both eyes. The Hess chart thus detects minor strength differences between the EOMs of both eyes, which are assumed to receive the same input following Hering's law of equal innervation.³⁹ Our data

suggest that such subtle differences in contraction force are more prevalent in MG than severe EOM weakness causing absolute duction limitations.

In addition to diagnosis, orthoptic measures could also benefit future clinical trials by quantifying the effect of novel treatments on EOM weakness in MG patients. Twenty per cent of MG patients develop a treatment-resistant ophthalmoplegia during their disease course and therapeutic strategies are lacking in this patient group, because a limited number of clinical trials have been performed for the treatment of ocular MG.⁴⁰ In recent clinical trials on new treatments targeting complement, the FcRn receptor and B-cells,⁴¹ purely ocular subtypes of MG were usually excluded, probably because the degree of ocular weakness has been difficult to quantify so far.^{42 43} More clinical research is therefore needed on the therapeutic management of ocular MG,^{2 44} and our data show that the extended orthoptic tests can be a sensitive and specific outcome measure to quantify the severity of EOM involvement in future clinical trials.

In future research, we suggest to perform the Hess chart measurements repeatedly with an interval of several weeks or months. This will likely provide insight on the fluctuation of the individual EOM involvement, as changes in affected EOM have been shown to be highly typical in MG.⁸ Therefore, we would also like to emphasise the value of structural documentation of

findings during bedside eye movement examination; the presence of ptosis and serial orthoptic testing and assess fluctuations in these findings. Additionally, it could further increase the diagnostic yield for the few patients that did not show drift on the Hess chart, as fluctuations are not likely in other causes of diplopia. Additionally, combining eye tracking methods using, for example video goggles⁴⁵ and the Hess chart to further quantify the drift phenomenon in MG patients over time could aid in an even more objective evaluation.

The main limitation of this study is that the included cohorts were not prospectively and consecutively recruited. Moreover, the examiner was not blinded to the diagnosis which may have biased the Hess chart and synoptophore measurements. However, drift was so apparent (see online supplemental videos) that we do not expect this to have influenced our main results. In addition, the test does not require any qualitative interpretation, and therefore, the quantitative measures are not likely to be influenced by knowledge of the diagnosis.

In conclusion, orthoptic measurements are valuable in identifying EOM fatiguability in MG. As drift was only present in MG, measuring persistent gaze using a Hess chart holds promise as a highly specific, non-invasive and easy to perform diagnostic test for MG. In addition, orthoptic measurements can be used to identify the severity of involvement of individual EOMs in MG, which may be a promising and clinically relevant outcome measure for clinical trials including ocular MG patients.

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Ethics approval This study involves human participants and was approved by the ethics committee that approved this study: METC Leiden Den Haag Delft (<https://www.ccmo.nl/metc/erkende-metc/metc-leiden-den-haag-delft>). The reference number for the ethics approval: P19.028. Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available on reasonable request. All data relevant to the study are included in the article or uploaded as online supplemental information. Anonymised data presented in this article will be made available at the request of a qualified investigator. Requests should be made to MRT (m.r.tannemaat@lumc.nl). Raw Hess charts and spider plots depicting the affected EOM per individual participant have been added as online supplemental data.

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