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Tracking Eye Movements for Diagnosis in Myasthenia Gravis: A Comprehensive Review

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Background: Around 60%—75% of myasthenia gravis (MG) patients initially present with nonspecific ocular symptoms. Failed recognition of these symptoms may delay the diagnosis of MG up to 5 years or more, leading to a reduced likelihood of remission and increased morbidity. Current diagnostic tests are either poorly sensitive for patients presenting with ocular symptoms alone or are time consuming, invasive, require a high level of technical expertise, and generally are universally difficult to obtain. This review will explore quantitative eye and pupil tracking as a potential noninvasive, time-effective, and less technically demanding alternative to current diagnostic tests of MG.
Evidence Acquisition: Comprehensive literature review.
Results: Thirty-two publications using oculography for the diagnosis of MG and 6 studies using pupillometry were evaluated. In MG patients, extra ocular muscle fatigue was evident in reports of intersaccadic, intrasaccadic and postsaccadic abnormalities, changes in optokinetic nystagmus, slow eye movements, disconjugate saccades, and pupillary constrictor muscle weakness.
Conclusions: Our review identified several potentially useful variables that derive from oculography and pupillometry studies that could assist with a timely diagnosis of MG. Limitations of this review include heterogeneity in design, sample size, and quality of the studies evaluated. There is a need for larger, well-designed studies evaluating eye-tracking measures in the diagnosis of MG, especially for patients presenting with purely ocular symptoms.

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Myasthenia gravis (MG) is an autoimmune disease affecting striated muscle neuromuscular junctions (NMJ), leading to variable, and commonly progressive, weakness of limb, bulbar, respiratory, and ocular muscles (1). While 60%–75% of MG patients present with ocular complaints (ptosis, blurred vision, diplopia, ophthalmoparesis) before developing generalized disease, 20% of patients persist with purely ocular symptoms (2,3). Diagnosis can be challenging due to several factors, including phenotypic variability, symptoms that overlap with other pathologies, and the poor sensitivity of current diagnostic tests.

Ocular dysmotility is the commonest cause of complaints as unique properties of extraocular muscles (EOM) increase susceptibility to autoimmune attack. They have a relatively lower depolarization safety factor due to less developed postsynaptic folding and therefore, lower concentrations of acetylcholine receptors (AChR), and restricted complement regulatory activity, leading to a higher risk of complement-mediated destruction (4). The strongest prognostic factor for remission in MG is thought to be disease duration at diagnosis, with symptom onset less than 1 year being the best predictor (5,6). Unfortunately, 14%–26% of patients are diagnosed more than 2 years post symptom onset and up to 13% more than 5 years (7–9). Diagnosing MG earlier improves remission rate reduces

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reliance on immunosuppressants and improves the quality of life (QOL) for patients.

EPIDEMIOLOGY AND PHYSIOLOGY

The prevalence of MG is between 70.6 and 179 per 1,000,000 individuals, with an annual incidence of 7.2–30.0 in 1,000,000 people (10–14). While the etiology of MG is unclear, it is thought to involve both genetic and environmental factors (15,16). The pathogenesis of MG involves a failure of thymus "self-antigen" recognition and the formation of autoantibodies (17). Aberrant antibodies include acetylcholine receptor antibody (anti-AChR Ab), found in 70%–80% of cases, muscle specific kinase antibody (anti-MuSK Ab), found in 1%–10%, and lipoprotein related peptide 4 antibody (anti-LRP4 Ab), found in 7%–32.7% of cases (2,18–20). These, along with many other potential target NMJ proteins, lead to dysfunction and eventual destruction of the NMJ via several mechanisms, including complement-mediated attack. This leads to impaired nerve-to-muscle ACh neurotransmission, causing variable and eventually progressive weakness (2,21). Symptomatic treatment is targeted at increasing NMJ ACh concentrations with acetylcholinesterase inhibitors. Disease modification requires the removal of circulating pathogenic antibodies via intravenous immunoglobulin or plasma exchange, immunosuppression (with steroids or steroid-sparing agents), and/or thymectomy (22).

Traditional Diagnostic Tests

Given the high frequency of ocular presentations, MG patients commonly present initially to the optometrist, ophthalmologist, or neuro-ophthalmologist. Diagnosis is dependent on a high index of suspicion, clinical examination, and paraclinical testing. Clinical tests, such as the Cogan lid twitch sign (23), the rest test, and ice tests, are not generally accepted as proof positive of MG, although the ice test has high sensitivity and specificity for ptosis secondary to MG (24–26). Currently, the most specific test for both ocular MG and generalized MG is blood serum anti-AChR Ab (18). However, up to 50% of ocular MG patients are seronegative (3). Anti-MuSK Ab can also be tested but is uncommonly found in isolated ocular MG (18). Repetitive nerve stimulation (RNS) has poor sensitivity for ocular MG (10%–29%) compared with generalized MG (53%–100%) (27,28), and it may cause patient discomfort (29). Intravenous edrophonium testing is no longer preferred because it requires intravenous access and cardiac monitoring, given its potential for significant cardiac side effects (30). Single fiber needle electromyography (SFEMG) has demonstrated high sensitivity (80%–100%) for detecting both ocular and generalized MG (3). However, jitter found on SFEMG, while strongly suggestive, is not specific for a neurotransmission disorder and can be seen in chronic progressive external ophthalmoplegia, oculopharyngeal dystrophy, and amyotrophic lateral sclerosis (31). SFEMG studies are extremely demanding on resources and dependent on a neurophysiologist with specific expertise, which is not always available (32,33). It may also cause discomfort, leading to poor test tolerance and inconclusive results (31,34).

Given the limitations of these traditional tests, there is a need to find a less invasive, time, and cost-effective test for the earlier diagnosis of MG, especially for those who present with purely ocular symptoms. Eye-tracking has been studied in MG but never translated into clinical practice. This review will evaluate existing findings and discuss the potential applications.

Basics of the Visual System

We depend on precise visual function for the accurate assessment of our environment. This involves precise independent internal and external ocular movements. Dysfunction will lead to visual disturbances. To ensure adequate acuity, target images must always remain within 0.5° of the fovea on the retina (35). Two mechanisms allow the eyes to do this: gaze stabilizing mechanisms (vestibulo-ocular reflexes, smooth pursuit, optokinetic reflexes) and gaze shifting mechanisms (visual fixation, saccades, and vergence) (35,36). A variety of structures within the cerebrum, brainstem, and cerebellum are responsible for these mechanisms (35).

Saccades are quick conjugate eye movements that bring the image of a target rapidly onto the fovea, changing the point of fixation (37). To produce a saccade, the eyes must quickly overcome the viscoelastic properties of the orbital tissues, which tend to keep the eyes centered in the primary position (38). A "burst of innervation" takes the eyes to their new position (measured by peak saccadic velocity, PSV). Then a "step of innervation" holds them in the new eccentric position. The pulse and step must be matched accurately, although there may be postsaccadic drift (or glissades) of the adducting eye during horizontal saccades, which may be normal in fatigued individuals (35,39). Maintenance of final eye position is dependent on tonic stimulation from supranuclear regions and on maintenance of neurotransmitter levels at the NMJ.

Saccadic eye movements of a specific type and amplitude have a highly consistent peak velocity–amplitude relationship (35,40). This relationship, over a range of amplitudes, is known as the saccade "main sequence" (40). Given the involvement of the NMJ in MG, the maintenance of peak velocity–amplitude relationships may be useful in differentiating MG from other causes of ophthalmoparesis.

Optokinetic nystagmus (OKN) is a normal physiological response, governed by both peripheral and central nervous systems, to large moving fields and consists of a slow phase when the eyes follow the target and a fast phase when they make saccade back to their original position (41,42). Disturbances in OKN, therefore, reflect either peripheral

(EOM muscle, vestibular, or cranial nerve) or CNS abnormalities (43).

The pupillary light response (PLR) exhibits a V-shaped response that can be divided into 3 periods (44). Period I reflects parasympathetic activity only, resulting in pupil constriction (maintained by signals from intrinsically sensitive photosensitive ganglion cells [ipRGC], rods, and cones) and can be measured in terms of latency of constriction onset, maximum velocity of constriction (VCmax), maximum acceleration of constriction (ACmax), and constriction amplitude. Period II represents a crossover period between sympathetic and parasympathetic innervation at the end of constriction and the beginning of dilation. As a light stimulus remains on, the pupil can stay constricted or can "escape" by dilating slightly. Period III reflects sympathetic activity only, with the pupil continuing to dilate (44). Theoretically, if the parasympathetic pathways of the PLR alone utilize ACh transmission, the ACh receptor–associated dysfunction in MG should only affect periods I and II (45).

EVIDENCE ACQUISITION

We performed a comprehensive literature review on both oculography and pupillometry in the diagnosis of MG. Published studies from the biomedical literature were found through PUBMED and EMBASE from the date of their inception to June 21, 2021. We identified 32 articles (Table 1) using oculography and 6 studies (Table 2) using pupillometry fitting the inclusion criteria. Please refer to **Supplemental Digital Content** (see **Supplemental Digital Content A**, http://links.lww.com/WNO/A617) for more detail.

RESULTS

Oculography in Myasthenia Gravis

Oculography Techniques

Four oculography techniques have been previously utilized in MG studies: electro-oculography (EOG) (46–49,51–54,61), magnetic search coil (MSC) (65–67,70–72), infrared oculography (IROG) (50,56–61,64), and video-oculography (VOG) (73,75,77). EOG uses electrodes placed near the eye at the inner and outer canthus to detect change in eye position, and although simple and inexpensive, it is prone to artifacts (83–85). It is no longer recommended for quantitative analysis of eye movement (85). MSC oculography remains the gold standard due to high accuracy, precision, range, bandwidth and linearity (85); however, recording is limited to 30 minutes to minimize corneal problems (83,86), and it is now used only for research (87). IROG measures infrared reflectance off the eyes, converting it into eye position information (85). While IROG is more accurate than EOG at detecting horizontal saccades (88), corrective lenses cannot be used (85). Continuous monitoring of lid blinks is also mandatory because blink artifacts may be indistinguishable from intrasaccadic or postsaccadic fatigue (60). Video-oculography (VOG) is now a popular method, in research applications, due to its accuracy and convenience (89). Although yet to be used in larger studies of MG (75,77), VOG has better angular resolution, and greater vertical and horizontal range than either EOG or IR-OG (90). Indeed, VOG performance approaches that of MSC (91). Importantly, VOG can be performed with both antireflective spectacles and contact lenses (90). For future MG oculography studies, VOG would be the most practical and reliable method to incorporate into clinical practice.

Oculomotor Tasks

The assessment task evaluates the capacity of muscles to generate a normal contraction force and to maintain it over time. Disease not only may manifest as abnormality of monocular motility parameters but also might affect binocularity/stereoscopy. Most studies in MG have evaluated the integrity of visually guided horizontal saccades, with amplitudes between 0.5 and 40° (49,51–58,60–68,71,72,75). Assessment of vertical saccades has only been conducted in those with vertical restriction (65–67,72). A few studies have also studied OKN (46–51,69,70), slow eye movements (74,76), smooth pursuit (77), and blink pattern and rate (73). Edrophonium was used in several studies to assess reversibility of neuromuscular blockade (56,58,62,69–76). Fatigue was tested using repetitive stimuli for OKN, whereas saccadic fatigue was tested using 20–30° repetitive refixations or eccentric gaze maintenance for 40 seconds to 8 minutes (51,52,64,67).

Saccades in Myasthenia Gravis

In MG patients, the PSV of horizontal saccades has been shown to be similar or increased compared with healthy controls and non-MG patients (52,61–63). While edrophonium increased PSV in MG patients, it decreased PSV in non-MG patients (49,51,52,65). Edrophonium also increased saccadic amplitude and induced hypermetria in MG patients (51,52,60,65). EOM fatigue resulted in intersaccadic variability, encompassing an array of different saccadic waveforms (52,56,58,61), and saccadic jitter (variability of PSV–amplitude relationship of saccades) (66), intrasaccadic fatigue (decrescendo, stutter, and slow eye movements) (58,60,63), and postsaccadic fatigue (wavering fixation and backdrift) (58,60,63).

The increased PSV–amplitude relationship post edrophonium suggests unmasking of underlying increases in central gain occurring to counteract EOM weakness (57,62,71). Increased central gain may also manifest as saccadic intrusions (56,62,68,71). The decreased PSV in non-MG patients is likely due to a weakened response of nonmyasthenic muscle after edrophonium (51,92). A normal PSV and amplitude in MG patients indicates that EOM fibers can respond normally at the beginning of the saccade, but a period of fatigue may lead to a reduction in these values (51,55,59). These findings alone are nonspecific and can overlap with other conditions causing

TABLE 1. Summary of included oculography studies

Author, Year and Study Design	OG	Task	MG(n)/Control† (n)	Method	Medication Status	Results
Blomberg & Persson, 1965 (46) Case control	EOG (ENG)	OKN	3/10	OK drum ± edrophonium	NA	Post-edrophonium increase in frequency and amplitude of OKN in MG.
Stella, 1967 (47) Case control	EOG (ENG)	OKN	4/4	OK drum ± edrophonium	NA	Post-edrophonium increase in frequency and amplitude in MG.
Campbell et al, 1970 (48) Case control	EOG (ENG)	OKN	17/18	OK drum 270–360 °/s. ± edrophonium	Variable	OKN amplitude decreases with successive beats. Variable between eyes. Post-edrophonium 6/17 responded, rest unclear or did not respond.
Metz et al, 1972 (49) Case control	EOG	VGS OKN	6/12	OK drum ± edrophonium	Withheld 48 h prior	PSV decreased and OKN amplitude and frequency reduced in MG. Reversed findings post-edrophonium
Spector et al, 1975 (50) Case control	IROG	OKN	16/15	OK drum ± edrophonium	Withheld <2 h in some	Post-edrophonium, OKN amplitude increased 24%–130%
Baloh et al, 1976 (51) Case control	EOG (DC)	VGS OKN	12/10	±3–30° Fatigue: 30° q1s, 8 min. ± edrophonium	Withheld 3–6 h prior	PSV decreased in some MG post fatigue
Yee et al, 1976 (52) Case control	EOG	VGS Pursuit	10/8	±20–40° Fatigue: 20 × 20°, for 40 s. ± edrophonium	Not stated	PSV WNL in MG, increased with edrophonium. PSV decreased in non-MG. Saccadic duration increased in MG depending on waveform. Waveforms in MG include normometric, hypometric, glissade-like and hypermetric (all non-specific). Saccadic latency WNL in MG. All patients unable to consistently match target >10°/s.
Mastaglia et al, 1976 (53) Case control	EOG (AC)	VGS	27/11	±25°, 1–2 q1s ± edrophonium	Not withheld	MSV decreased in 14/27 MG. Edrophonium increased velocities in 10/16 MG, and in 1 MS patient.

(Continued)

Author, Year and Study Design	OG	Task	MG(n)/Control† (n)	Method	Medication Status	Results
Mastaglia et al, 1977 (54) Cross sectional	EOG (AC)	VGS	25/0 No controls but looked at MS patients in same study.	±25°, 1–2 q1s. ± edrophonium	Not withheld	MSV decreased in 14/25 MG. Post-edrophonium, MSV increased in 10/14 MG.
Spooner & Baloh, 1979 (55) Case study	EOG	VGS	1/0	±30°, q1sec, for 3 mins. ± edrophonium	Not stated	PSV-amplitude decreased with repetitive fixations. Edrophonium normalised PSV, recovered dissociated nystagmus and adducting muscle weakness.
Schmidt et al, 1980a (56) Cross sectional	IROG	VGS	10/0	±20° or less depending on patients' paresis, 1 q2s for 3 min	Withheld between 2 and >12 h prior	7 waveforms identified: Normal (n), slow (s), overshoot with glissadic return (o), undershoot with glissadic tail (u), dynamic overshoot (do), multiple closely spaced saccades (m) and discrete deceleration (dd). Schmidt also used the terms "orthometric (O)," "hypermetric (HR)," and "hypometric (HO)" to describe the final eye positions after completion of saccades.
Schmidt et al, 1980b (57) Cross sectional	IROG	VGS	10/0	Fixation 20° or less, to the right 3 min. Then alternating fixation between 3 targets (left, centre, right) for 3 min, then 3 min leftward gaze and equal amount of refixations. ± edrophonium	Withheld between 2 and >12 h prior	PSV supernormal in MG. Refixations produced no significant changes in amplitude, but intrasubject gain was normal. Maintained gaze led to nystagmus with dynamic overshoots in 6/10.3/10 had double saccadic pulses. 4/10 had little response post refixations after maintained gaze. 6/10 had other changes (muscle fatigue, rest-effect, increased saccadic gain, paradoxical response).
Feldon et al, 1982 (58) Cross sectional	IROG	VGS	5/0 No controls but also looked at 3 GBS patients	Degree not stated 150 responses recorded.	Withheld	Intrasaccadic fatigue (decrescendo, stutter, slow movements), post-saccadic fatigue (backdrift and waver) in both MG and GBS groups

(Continued)

Author, Year and Study Design	OG	Task	MG(n)/Control‡ (n)	Method	Medication Status	Results
Williams et al, 1986 (59) Cross sectional	IROG	VGS	26/0 (suspected MG)	±10° Fatigue: gaze 30° one side for 2 mins prior to recording a 10° saccade from centre to same side. ± edrophonium	Not stated	10/13 patients with a positive edrophonium IROG test had subsequent diagnosis of MG. 13 patients had a negative IROG test, none of which had MG. Edrophonium prevented fatigue in 50% of patients who had a 10% reduced amplitude post-fatigue but pre-edrophonium (8/26).
Sollberger et al, 1986 (60) Case control	IROG	VGS	22/20	±30°, q1.5s for 2 mins. ± edrophonium	Not stated	IROG abnormal in all ocular MG, 80% generalised and in 33% of generalised non-ocular patients. Intrasaccadic, post-saccadic and intersaccadic abnormalities in MG. Fatigue accentuates latent pathology in 17/22. Edrophonium causes hypermetria or abnormal increase in saccadic amplitude.
Yee et al, 1987 (61) Case control	EOG/ IROG	VGS	42/73	±10, 20, 30° ± edrophonium	Not stated	PSV was normal in 72%–79% MG. No significant difference to healthy controls, significantly different to CPEO and CNP (slower). Saccadic waveforms were hypometric, hypermetric, biphasic.
Oohira et al, 1987 (62) Case study	High speed XY tracker	VGS*	1/0	±5–20°	Saccades recorded 1-month prior treatment, then after treatment.	PSV varied in both eyes before treatment but decreased in both eyes after treatment. Supernormal velocity occurred in abduction and adduction of right eye before treatment. Saccadic gain varied between the 2 eyes. The right eye remained constant pre and post-treatment, the left eye decreased to normal after treatment.

(Continued)

Author, Year and Study Design	OG	Task	MG(n)/Control‡ (n)	Method	Medication Status	Results
Tedeschi et al, 1991 (63) Case control	EOG (DC)	VGS	21/160 (Suspected MG)	±2–40°, q1sec	Not stated	PSV mostly normal or increased in MG (except 2). Intrasaccadic, post-saccadic abnormalities found in MG. Edrophonium had a positive effect in 11/16 MG. only 1/5 purely extraocular MG had abnormal EOG, whereas almost all patients with ocular involvement had abnormal EOG.
Oey et al, 1992 (64) Cross sectional	IROG	VGS	32/0 (Suspected MG)	Small saccades (±10°), large saccades (±20°) Fatigue: ± 20°, q1.5s, for 5 mins. ± edrophonium	Withheld 48 h prior	SFEMG of orbicularis muscle showed greater correlation than IROG and RNS with MG.
Barton et al, 1994 (65) Case control	MSC	VGS*	8/12	±20°, q1s, for 8.5 mins. Vertical ±20° for those with vertical limitations of movement ± edrophonium	Withheld 24 h prior for ocular MG, morning dose for generalised	Edrophonium causes can increase in saccadic asymptotic peak velocity (Vmax) in MG patients. In non-MG and healthy participants Vmax decreased and peak velocity–amplitude curve shifted downwards.
Barton & Sharpe, 1995a (66) Case control	MSC	VGS*	9/12	±20°, q1s, for 8.5 mins. Vertical ±20° for those with vertical limitations of movement ± edrophonium	Withheld 24 h prior for ocular MG, morning dose for generalised	Saccadic jitter: Variability of peak-velocity amplitude relationship of saccades (RMSE) increases in MG cf. non-MG. However, there is overlap of data from MG and non-MG patients at lower values of SJ.
Barton et al, 1995b (67) Case control	MSC	VGS*	8/11	±20°, q1s, for 8.5 mins. Vertical ±20° for those with vertical limitations of movement. ± edrophonium	Withheld 24 h prior for ocular MG, morning dose for generalised	Saccadic duration was increased in MG and non-MG cf. normal. Deceleration time increased in MG and non-MG compared to normal subjects, but not different between groups. Edrophonium decreased saccadic duration in MG, whereas increased in non-MG and normal subjects

(Continued)

Author, Year and Study Design	OG	Task	MG(n)/Control† (n)	Method	Medication Status	Results
Komiyama et al, 1999 (68) Case study	EOG (AC)	VGS*	1/0	±10° ± edrophonium	Withheld 24 h prior	Saccades were hypermetric with quiver. Edrophonium evoked macrosaccadic oscillations within 30 s
Toth et al, 1999 (69) Case control	EOG (ENG)	OKN	17/12	Langne generator at 10, 20, 30°. Recorded on paper 10 mm/s	Withheld 12 h prior, and tested 1 h after taking	OKN slow phase angular velocity reduced, especially at 30°. Pyridostigmine increased velocity but did not reach control level.
Yang et al2000 (70) Case control	MSC	OKN	16/12	Computer generated grating, 36° horizontal and 27° vertical	Withheld 24 h prior	Open-loop OKN gain more sensitive than closed loop. Open-loop gain lower than in normal group, showed a significant increase in gain post anti-cholinesterase. No changes occurred post-drug administration for normal and non-MG groups
Sander et al, 2008 (71) Case control	MSC and video based	VGS Pursuit	1/29	Small amplitude ±0.5–3°, large amplitude ±10–15°. Pursuit method NA.	Not stated	Saccadic velocity increased in MG cf. control. Waveforms were hypermetric with dynamic overshoot. Disjunctive binocular movements were seen. Pursuit interrupted by square wave jerks (SWJ), but also present in controls. SWJ faster than controls.
Serra et al. 2008 (72) Case control	MSC	VGS*	22/10	±5–40°	Not stated	Binocular phase plane analysis revealed the initial components of horizontal saccades from the MG patients were like controls. They only showed disconjugacy later during saccades. Patients with true INO and abducens nerve palsy showed early velocity disconjugacy within the first 10% of eye displacement and remained abnormal throughout the movement

(Continued)

Author, Year and Study Design	OG	Task	MG(n)/Control‡ (n)	Method	Medication Status	Results
Azri et al, 2014 (73) Case control	PRILIB	Blink	4/10	Task 1. Read a newspaper for 20 mins, then 5 min break Task 2. Watch 90 min long movie. Lights turned off	Not stated	MG patients blink more and showed more palpebral aperture fluctuations than healthy controls
Liang et al, 2016 (74) Case control	EOG (DC) Sleep study	Horizontal SEM	8/8	MWT on first day with overnight PSG, then MSLT second day. Horizontal and vertical movements detected. Data analysed only from awake periods for first 10 minutes	Not stated	MSLT and PSG showed higher quantity of average slow horizontal eye movements in MG cf. control MWT no differences.
Rutkove & Malik, 2017 (75) Case control	VOG	VGS	1/1	±20° maintained gaze 1 min	Not stated	MG patient was unable to maintain fixed gaze, with visual "jitter" and slow non-synchronous drift of both eyes. No diplopia symptoms.
Liang et al, 2019 (76) Case control	EOG (DC) Sleep study	Horizontal SEM	8/31	Separate recordings from PSG AND MSLT from same patient were treated as independent samples. 7 hours recorded, but first 10 min studied only.	Not stated	EOG based signal analysis using the Rise rate feature has the best MG classifier ability
Chae et al, 2019 (77) Case studies	VOG	Pursuit	2/0	20° movements for 5 mins Neostigmine given after initial test	Not stated	There was an increase in smooth pursuit gain over time, in addition to quiver eye movements and glissade-like waveforms. Neostigmine resulted in a recovery of these findings.

All studies of visually guided saccades (VGS) and OKN were horizontal unless specified otherwise.
±Left or right saccades.
*Horizontal and vertical saccades.
†With and without edrophonium.
‡Controls include healthy or non-MG participants, or both.
CNP, cranial nerve palsy; CPEO, chronic progressive external ophthalmoplegia; EOG, electrooculography; INO, internuclear ophthalmoplegia; IROG, infrared oculography; MG, Myasthenia Gravis; MSC, magnetic search coil; MSV, mean saccadic velocity; OG, oculography technique; OKN, optokinetic nystagmus; PRILIB, portable real time infrared lids, iris and blink system; PSV, peak saccadic velocity; VGS, visually guided saccade; WNL, within normal limits; RNS, repetitive nerve stimulation; SEM, slow eye movements; SFEMG, single fibre electromyography; VOG, video-oculography.

TABLE 2. Summary of included pupillometry studies

Author, Year, and Study Design	Device	MG(n), Controls (n)	Method	Medication Status	Results (in MG)
Yamazaki et al, 1976 (78) Case control	IR, silicon-vidicon camera (HTV-N-248)	7 MG (6 ocular 1 generalised) 5 controls	Right eye. Sinusoidal (0–0.0075 mW, 0.25–3.0 Hz), Pulse 0.05 mW for 1 s, q5s	2 on steroids *Not withheld*	Latency of pupillary constriction onset was prolonged. Pupillary constriction amplitude and ACmax were reduced.
Lepore et al, 1979 (79) Case control	Slit lamp (Zeiss) and biomicroscope	25 MG (0 ocular 25 generalised 35 controls (25 healthy, 10 non-neurological taking steroids)	Both eyes tested for 100 oscillations with 0.5 mm horizontal slit beam. Target fixation distance, no correction 6m.	2 no treatment 6 AChE inhibitors, 11 prednisolone, 6 AChE and prednisolone. *Not withheld* *13 had thymectomy	Pupil reflex cycle time (PRCT) was prolonged in MG patients compared to controls.
Dutton et al, 1982 (80) Case control	Slit lamp (Heig-Streit)	12 MG (3 ocular 7 generalised) 12 controls	Right eye. 10 min continuous 0.5 mm horizontal slit beam	11 pyridostigmine, 2 steroids. *Not withheld*	PRCT and oscillation frequency were both reduced.
Lu et al, 1985 (81) Case control	IR	36 MG (15 ocular 21 generalised) 22 healthy controls, 6 neurosis, 7 muscular dystrophy (MD), 16 motor neuron disease (MND)	Left eye. 15 lux illumination at 2.2 m = 72.6 cd/$m^{2.}$ Target fixation distance 30 cm.	21 AChE inhibitors, 2 steroids, 13 AChE inhibitor and steroids. *AChE inhibitors withheld 1-2 doses prior*	Latency of pupillary constriction onset was prolonged and pupillary constriction amplitude was reduced
Tsiptios et al, 2008 (45) Case control	IR, CCD high speed digital camera. Sampling rate 262 Hz	16 MG 16 controls	Both eyes. 5 stimuli at 24.6 cd/m^2 for 20 ms q30s. Target fixation distance 1.5 m	NA	Latency of pupillary constriction onset was prolonged. Pupillary constriction amplitude, ACmax and VCmax were reduced.
Kaltsatou et al, 2015 (82) Case control	IR, CCD high speed digital camera	32 MG (mild) 33 controls	Both eyes. 5 stimuli at 24.6 cd/m^2 for 20 ms q30s. Target fixation distance 30 cm	NA	Latency of pupillary constriction onset was prolonged. ACmax and VCmax were reduced.

AChE, acetylcholinesterase; AChR-Ab, acetylcholine receptor antibody; ACmax, maximum acceleration of pupil constriction; CCD, charge-coupled device; Cd/m^2, candelas/m^2 (intensity); IR, infrared; MG, Myasthenia Gravis; NA, not available; PRCT, pupillary reflex cycle time; RNS, repetitive nerve stimulation; SFEMG, single fibre electromyography; VCmax, maximum velocity of pupil constriction.

*Significance only applies to those with generalised MG, not those with ocular MG.

ophthalmoparesis. However, the combination of variable waveforms with intersaccadic variation occurs mostly with disorders of neurotransmission (64).

Saccadic duration abnormality was generally a nonspecific finding (51,52,58,67). However, post edrophonium, saccadic duration reduced only in MG patients, which may allow differentiation of MG from other conditions (67). MG patients also demonstrated disjunctive saccades where initial components of horizontal saccades were like healthy controls but showed disconjugacy later during saccades (71,72). In contrast, true INO and abducens nerve palsy show early velocity disconjugacy within the first 10% of eye displacement (71,72). Quiver eye movements (small amplitude, corrective, hypermetric saccades with supranormal PSV) in MG patients can also occur even in cases of severe ophthalmoparesis and limited eye movement (52,61,63,68,77).

Overall, a single or averaged PSV–amplitude measurement alone for the diagnosis of MG is unreliable due to overlap with other patient groups demonstrating a spectrum of recorded values, such as thyroid eye disease (61). Qualitative measures in isolation such as waveform and description of saccadic fatigue phenotypes are useful but difficult to translate into diagnostic criteria. Quantification of saccadic jitter is promising but is based on only one small study. It has high specificity of 95% but could only detect 42% of MG patients. A larger study is needed to determine if a higher sensitivity can be achieved. In addition, in the absence of edrophonium use, oculography studies will need to depend more on fatigue testing to evoke abnormalities in future. Variability of saccade trajectory and loss of binocularity may also provide diagnostic clues.

Optokinetic Nystagmus

In MG patients, OKN was characterized as low amplitude, frequency, and slow-phase angular velocity, which worsened with fatigue and improved post edrophonium (48–50,69). A change in OKN amplitude was found to be more sensitive than frequency, as was using IROG and an open-loop method (50,70). However, OKN is challenging to measure and prone to misinterpretation. Challenges include ensuring a synchronous response with target speed not exceeding 30°/sec and frequency around 2 Hz (93), as well as ensuring that participants are kept alert (94), consistently either "looking" (subcortical pathway) or "staring" (cortical pathway) at the OK drum (94,95) and that they are not exposed to vibration or auditory stimulation (96). Habituation of OKN amplitude (smaller OKN in anticipation of the next stimulus) can also occur in both MG and healthy subjects (48).

Other Findings

During sleep studies, MG patients demonstrated more horizontal slow eye movements (SEM), compared with controls (74). Patients also had a higher blink rate and variability in palpebral aperture fluctuations than controls (73). Given that healthy adults can also exhibit an unexpectedly high spontaneous blink rate (97), these findings are not specific to MG. Similarly, smooth pursuit gain reductions seen in MG patients during fatigue testing (52,71,77) and are nonspecific (35). Although square wave jerks with dynamic overshoot have also been found to interrupt smooth pursuit in MG patients, this was only observed in a single case study (71).

Pupillometry

A slit-lamp (79,80) or infrared (45,78,81,82) pupillometry was used in studies of MG patients. Some studies ensured 8 hours of sleep (45,82), and some implemented a period of dark adaptation of either 2 or 15 minutes before testing (45,78,82). Fixation points varied between 30 cm and 6 m. AChE inhibitors were also used to elicit any reversibility (78,81).

In MG patients, mean pupillary radius and area after a period of dark adaptation was similar to controls, as was pupillary constriction deceleration (45,78). Pupillary constrictor muscle involvement was identified by reduced amplitude of pupillary constriction with repetitive stimulations (78,81), decreased pupillary oscillation frequency (80), prolonged pupil cycle reflex time (PCRT) (79,80), reduced ACmax, and reduced VCmax (45,78,82).

In MG patients, the latency of pupillary constriction onset and time to maximum constriction were found to be prolonged compared with controls (45,78,81,82). A prolonged latency to onset may be due to attenuated neurotransmission; however, latency also increases with decreasing stimulus intensity, increasing age, and retinal–neuronal pathway dysfunction (98,99). Pupillary dilator weakness was reported but not universally identified (45,78,81). Lack of effect might have been predicted based on their sympathetic innervation. However, weak immunoreactivity muscarinic receptor types 1 and 5 have been found on dilator muscles (100), in keeping with previous findings that the dilators are intermediate between striated muscle and epithelial tissue, whereas the constrictors are transformed into smooth muscle (101). This suggests that both muscle groups may be affected in MG due to cross-reactivity of antibodies, although this is yet to be proven. AChE inhibitors led to variable reversibility or no changes of PLR parameters between studies (78,81). Overall, the physiological basis of the PLR dysfunction in MG is still debatable.

Pupillary constrictors are classified as smooth muscle, derived from neural ectoderm and harbor muscarinic AChR at their NMJ (particularly M3, 60%–75%) (102). Skeletal muscle is derived from mesoderm and express nicotinic AchR (103,104). Given these differences, there is unlikely to be a direct cross-reaction with AChR-Ab between the two. However, it may be that there is cross-reactivity of other undetectable antibodies against antigens that are present in both skeletal and iris constrictor muscle NMJs (18). Furthermore, PLR dysfunction may not occur at the level of the NMJ. There are different subtypes of nicotinic

receptors, and some serve in interneuronal transmission of the PLR and may conceivably be affected by circulating AChR-Ab measured in extremely low titers in the cerebrospinal fluid, although we normally associate the antibodies with effect on muscarinic receptors (103,105) as underlined by studies that have found that nicotinic neuronal AChR does not interact in vitro with skeletal muscle AChR-Ab (105).

The classic diagnostic marker of MG is variability and fatigue in muscle contraction. This is not clearly addressed in pupillometry studies to date. If there is NMJ or interneuronal fluctuation in ACh availability, we would expect moment-to-moment variability in PLR parameters. PRCT has not offered insight into these characteristics because it is calculated as an average of cycles at a single timepoint using 5-pulse stimuli (45,78,82). This may not represent sufficient sampling to characterize variability or fatigue. The study of oscillation frequency did not comment on whether the amplitude of the oscillations decreased over time, which would more strongly suggest fatiguability, rather than frequency (80). Intersubject variability of PLR morphology was also not discussed (45). This could be explored in future studies, using a higher frequency stimulus to elicit fatigue and variability observed in the response profile. Intermittent stimuli rather than a long duration stimulus could also elicit a stronger and more sustained pupillary constriction compared with continuous light, which is prone to a pupillary escape profile (106). All studies used a white light stimulus, which excites rods, cones, and ipRGCs, which all contribute to the initial constriction response. However, an early pupillary escape occurs due to waning of the rod–cone contribution over time, which may be misinterpreted as fatigue. Monochromatic stimuli, such as blue light, may be helpful in looking at variability and fatigue because the contractions by ipRGC are more sustained. Finally, most of these studies used customized pupillometers not readily accessible for clinical use. Using a commercially available pupillometer, such as the NeurOptics NPi-200 or RAPDx (Konan Medical) in future research, may facilitate translation into clinical practice (107).

CONCLUSION

MG remains a diagnostic dilemma for many clinicians, especially in those with initial ocular involvement. Traditional diagnostic tests fail to detect MG in patients with purely ocular symptoms, whereas others are invasive, time consuming, and require a high level of expertise to administer. We acknowledge that this review is limited by studies with small numbers of participants and aged or equipment that has not been universally available. We suggest that further larger studies are required to understand how eye-tracking and pupillometry can characterize diagnostic abnormalities in patients with MG. Modern eye-tracking technologies, such as VOG, hold great promise as a means of diagnosing MG. Although some centers may need to acquire VOG equipment, and clinicians will need to be trained to test and interpret the results; the advantages is that it will be a noninvasive, time-efficient, and cost-efficient method. It may allow for earlier diagnosis with a reduction in morbidity and mortality.

STATEMENT OF AUTHORSHIP
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