# The use of the Saccadometer to identify saccadic characteristics in Myasthenia Gravis: A Pilot Study.

Craig Murray (MRes)[1], David Newsham (PhD)[1], Fiona Rowe (PhD)[1], Carmel Noonan (MB BCh, FRCOphth)[2] and Ian Marsh (MB BCh, FRCS Ed, FRCOphth)[2]

1. University of Liverpool, UK
2. Liverpool University Hospitals NHS Foundation Trustf4nleyten
3.

Corresponding author:

Craig Murray

University of Liverpool

School of Health Sciences

Thompson Yates Building

Brownlow Hill

UK

L69 3GB

craigm@liverpool.ac.uk

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Abstract

Background

Myasthenia gravis often presents with ocular signs that mimic other forms of ocular defects such as isolated cranial nerve palsy. Normal velocity or even hyperfast saccadic eye movements in the presence deficits of smooth pursuit has been well described in the literature in myasthenic patients. The reason for these paradoxical clinical findings has been reported to be due to increased post-synaptic folding of the fast-twitch fibres responsible for the execution of a saccade which is absent in those fibres responsible for slower, smooth eye movement. Saccadic characteristics therefore offer a point of differential diagnosis between patients suspected of having ocular motility deficits as a result of myasthenia gravis and those caused by other neuropathies. The advent of portable quantitative saccadic assessment means that previously laboratory based assessments that require specialist equipment and training may now be undertaken clinically, providing a non-invasive test that can aid the differential diagnosis of the condition. The aim of this pilot study is to investigate the feasibility of the Saccadometer (Ober Consulting) in detecting the saccadic characteristics associated with myasthenia, specifically normal peak velocity in a group of confirmed myasthenia patients.

Methods

A group of five patients with a confirmed diagnosis of myasthenia gravis recruited form a single site were recruited into the study a long with five age matched healthy volunteers. All myasthenic patients had ocular signs such as under-action or limitations of motility confirmed through ocular clinical examination. Healthy volunteers were screened for any underlying ocular motility or neurological defects prior to inclusion within the study. All participants undertook 100 trials of both $10^{\circ}$ and $20^{\circ}$ amplitude saccades and mean peak velocity, amplitude and latency was recorded using the Saccadometer for each individual. Overall mean peak velocity, amplitude and latency was collated for the both myasthenic and healthy control groups for each saccade size and compared.

Results

Mean peak velocity was significantly greater (481 deg/sec ±103.5), for myasthenic patients compared with healthy controls (384 deg/sec ±42.8) ($p<0.05$) in 10 $^{o}$ saccades. Peak velocity was also greater in myasthenics for 20 $^{o}$ saccades, however this difference did not reach statistical significance for MG patients (547 deg/sec ±89.8 vs 477 deg/sec ± 104.5) ($p = 0.14$). The latency of MG participants was not significantly different from those of age matched healthy participants in 10 $^{o}$ saccades but was significantly different for 20 $^{o}$ saccades. There was no difference in amplitude measured between the groups.

Conclusion

Peak velocity for both 10 $^{o}$ and 20 $^{o}$ saccades was greater in myasthenic patients compared with healthy controls. All myasthenic patients produced normal velocity saccades in the presence of deficits of smooth ocular motility. The results from this small pilot study demonstrates the potential use of the Saccadometer in a clinical setting to provide a non-invasive aid to diagnosis of suspected myasthenia patients.

**Background**

Myasthenia Gravis (MG) and in particular ocular myasthenia gravis (OMG) remains a diagnostic challenge. Confirmation of diagnosis is important in order for patients to begin the appropriate treatment that will alleviate debilitating symptoms such as fatigue, muscle weakness or diplopia. Furthermore, there is evidence to suggest that that early intervention with the appropriate medication can slow and even prevent the progression to General Myasthenia Gravis (GMG).[1&2]

Diagnosis most often relies on the detection of acetylcholine antibodies (AChR) in blood serum testing. However, patients may present with the clinical characteristics of MG, yet have a negative response to AChR testing. Positive AChR response is reported to be only 80-85%[3&4] of GMG patients, reducing to 55-70% in patients presenting with the condition in OMG. [3&4]

Ocular characteristics, commonly diplopia and ptosis, are the initial presenting symptom in 65- 90% of patients[3-5] with 85% going on to develop GMG within three years of onset.[6] Up to 80% of MG patients present with ocular features of the condition either as the first sign of the disease or at some point during the disease course.[5] There are a number of techniques currently in use to diagnose MG. Single Fibre Electromyography (SFEMG) has high sensitivity in detecting abnormal neuromuscular transmission[7-10] and has therefore been used clinically in the diagnosis of MG over the last 20 years. However, this technique requires specialist equipment and expertise that is not available at all hospital sites. Furthermore, although SFEMG may be sensitive for MG, the test is less specific and there are reports of false positive results in patients with conditions not related to MG.[2] Sensitivity of Edrophonium Chloride has been reported at 86-92% for OMG and 88-95% in GMG. [11, 12] However, there are reports of false positive results in other neurological conditions such as motor neurone disease and brainstem tumours[13, 14] and the assessment is invasive with potentially severe side-effects. The ice test[15-17] and the rest test[18] have been used clinically to aid the diagnosis of the disease, particularly when ptosis is the main feature in OMG. The ice test however, is less effective

when the extraocular muscles (EOM) are primarily affected[17] meaning it is only possible to confirm the diagnosis of MG in those patients that present with ptosis.

The relationship between saccadic amplitude and velocity is described by the M-sequence. [20] As saccadic amplitude increases so too does peak velocity in a uniform positive correlation, meaning that for a given size of saccade, the peak velocity is accurately predictable. In a disease process that affects the extraocular muscles, or the control of these, in order to produce a fast or slow eye movement it can be expected that this relationship would be disrupted. However, the presence of normal velocity or hyperfast small saccades where there are clinically detectable underactions and/or limitations of smooth pursuit is unique to MG and has been demonstrated to provide a potential point of differential diagnosis of MG from other neurological conditions that the disease may imitate.[21-24] This indicates quantitative assessment of saccades offers an additional diagnostic avenue to confirm the presence of MG.

Equipment used in these studies and in the majority of studies that explore quantitative eye movement measurement are most often table top based systems that require specific expertise in order to use them and are primarily used in research rather than a clinical setting in the UK. This means that clinical access to this type of testing in order to aid diagnosis is limited. The advent of portable systems that are compact enough for use in the clinical setting or at the bedside providing a more flexible, non-invasive means of quantitative eye movement assessment could enable clinical detection of the unique saccadic characteristics at an earlier stage. Systems such as the Saccadometer™ (Ober Consulting) produces automatically produce quantitative data relating to saccadic parameters such as velocity, amplitude and latency and does not require in-depth training in order for individuals to use them.[25] The aim of this pilot study therefore was to explore the feasibility of using the Saccadometer as a diagnostic tool to detect the saccadic characteristics in MG patients.

**Methods**

A power calculation was performed indicating a total of 5 patients was sufficient for this study Local ethical approval was obtained in line with and Tenents of the Declaration of Helsinki were followed. Informed consent was obtained from all participants and any individual was able to withdraw consent at any time during the study.

The Saccadometer automatically produces individual and mean calculations of saccadic parameters for each participant across a set number of trials. The number of trials undertaken for both 10 and 20 degree amplitude saccades in this study was 100. Mean peak velocities for 10 and 20 degree amplitude saccades were collated into mean peak velocities (±SD) for MG patient and healthy control groups. These results were then compared using two sample t-tests. The same analysis was performed for both saccadic latency and saccadic amplitude. Analysis of variability in mean peak velocity between and within participant groups was performed using the f-test.

*MG Participants*

Patients with confirmed MG were recruited from the Ophthalmology Department of Aintree Hospital, Liverpool UK. Inclusion criteria for MG patients was as follows:

- Confirmed diagnosis by positive AChR test or by positive SFEMG
- Clinical presentation of extraocular muscle weakness including underactions and/or limitations of movement attributed to MG
- Age 18 or older

Exclusion criteria:

- History of eye movement disorder associated with any other neurological condition
- History of mechanical or restrictive ocular motility disorder
- History of concomitant strabismus

Age matched healthy control participants were recruited and screened for participation through advertisement at the University of Liverpool and met the following inclusion criteria:

- Aged 18 years of age or older.
- Visual acuity of ≥1.0 logMAR

Exclusion criteria:

- History of extra-ocular muscle abnormality or concomitant strabismus
- Ocular motility anomaly identified during screening
- History of auto-immune disease, specifically diabetes, Chronic Progressive External Ophthalmoplegia or Thyroid Eye Disease.

*Saccadic Task*

The Saccadometer is a head mounted device, which projects laser points to any blank surface situated between 1m and 3m from the participant. The device uses reflective photographic infra-red oculography to measure the saccadic amplitude, velocity and latency for each individual trial. Horizontal visual reflexive saccades of $10^{o}$ (100 trials) and $20^{o}$ (100 trials) amplitude were recorded using the Saccadometer in all patients. Once complete, recorded data was transferred from the Saccadometer to a laptop containing the accompanying software (latency meter) for analysis. An example trace for one trial can be seen in figure 1.

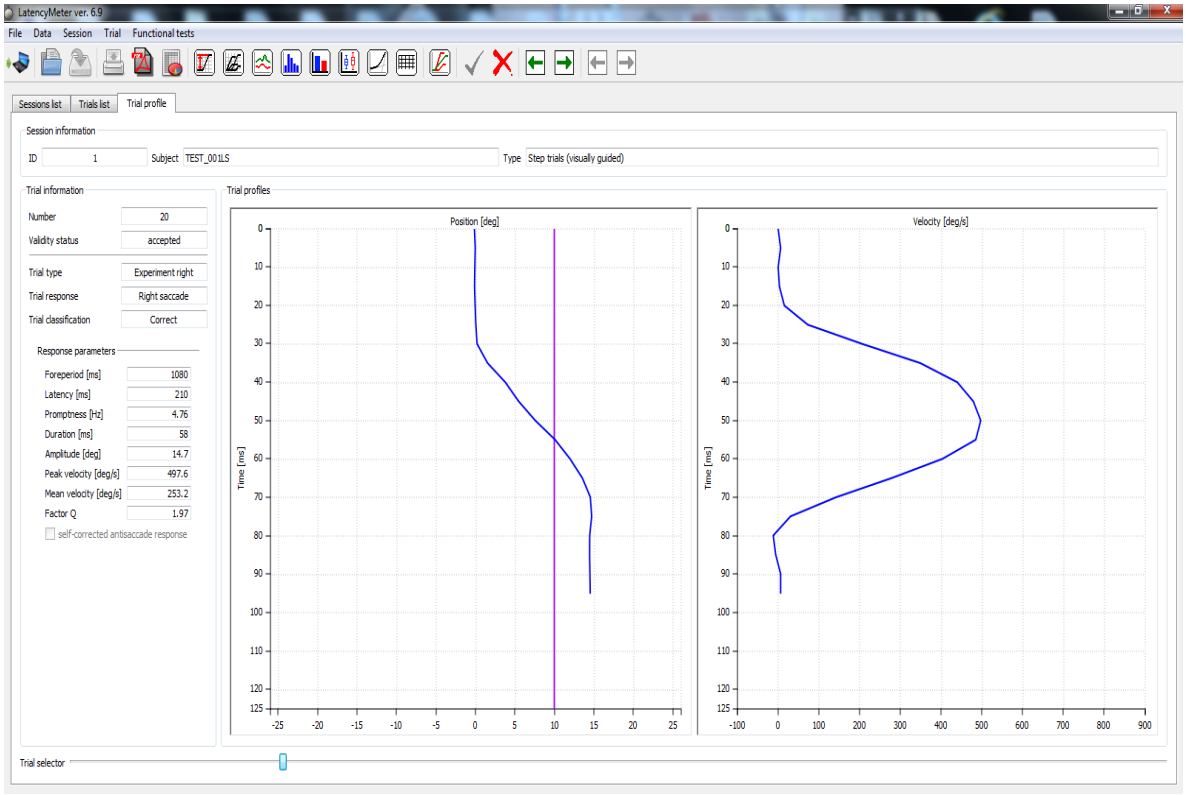



*Figure 1: Trace of a single saccadic trial produced via the Saccadamoter and accompanying Latencymeter software from MG participant 4. The software additionally provides mean ±SD result for all saccadic trial undertaken for each participant.*

**Results**

Five confirmed MG patients were recruited along with five age matched healthy controls; participants were grouped by age bandings of ten years. All five MG patients were confirmed through a positive AChR antibodies test. The demographics of the groups can be seen in Table 1. All five MG patients had ocular motility deficits in the form of horizontal recti underactions or limitations (Table 2), one patient also had mild ptosis.

| | Age (m/f) | |
|---|---|---|
| Participant ID | MG Patient | Control Participant |
| 1 | 91 (m) | 85 (m) |
| 2 | 64 (f) | 61 (m) |
| 3 | 76 (m) | 71 (f) |
| 4 | 55 (m) | 51 (m) |
| 5 | 68 (m) | 62 (f) |
| Mean (±SD) | 70.8 (±13.6) | 66.0 (±12.8) |
| Age range | 55-91 | 51-85 |

*Table 1. Demographics of MG patients and age matched control groups, m = male, f = female.*

*Peak Velocity*

Mean peak velocity (PV), latency and amplitude for 10° and 20° saccades in MG patients and age matched heathy controls are illustrated in Table 2. Mean PV (±SD) of 10° and 20° saccades for individual MG patients and healthy controls are illustrated in Figures 1 and 2. Figure 3 illustrates the combined PV performance for the five MG participants and the five control group along with the mean PV for each group.

For 10° saccades, mean PV for MG participants was significantly greater (481 deg/sec ±103.5), compared to controls (384 deg/sec ±42.8) ($p<0.05$). Individually, patients 1-3 produced faster saccades than their age matched healthy volunteers. Additionally, when compared to normal saccadic parameters described by the M-sequence (300 deg/sec), MG patients produced significantly faster 10° saccades ($p<0.01$).

Mean PV values were greater for MG patients (547 deg/sec ±89.8) compared with healthy controls in 20° saccades (477 deg/sec ± 104.5); however, this difference was not statistically significant ($p = 0.14$). Mean PV for 20° saccades was significantly greater ($p<0.01$) in this group when compared with normal saccadic parameters described by the M-sequence (400 deg/sec).

Table one also documents the standard deviations for each group of controls and healthy controls. There was no statistically significant difference between MG subjects in 10° (±103.4) and 20° (±89.9) saccades ($f = 1.32$, $p = 0.40$) nor between these two amplitudes for healthy controls (±42.8, ±104.5; $f=0.17$, $p = 0.05$). There was also no statistically significant difference in variance between MG and healthy controls in 10° saccades (±103, ±42.8 respectively) ($f = 5.8$, $p = 0.06$) or in 20° saccades (MG, ±89.8; healthy controls ±104.5) ($f = 0.7$, $p = 0.39$).

| | | Mean PV 10 deg | | Mean Latency 10 deg | | Mean Amp 10 deg | | Mean PV 20 deg | | Mean Lat 20 deg | | Mean Amp 20 deg | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ID | MG Motility | MG (deg/sec± SD) | Con (deg/sec± SD) | MG (ms±SD) | Con (ms±SD) | MG (deg±SD) | Con (deg±SD) | MG (deg/sec± SD) | Con (deg/sec± SD) | MG (ms±SD) | Con (ms±SD) | MG (deg±SD) | Con (deg±SD) |
| 1 | ptosis, bilat LR u/a | 567(±209) | 355 (±84) | 218(±40) | 167 (±38) | 7.2 (±1.6) | 8.0 (±2.6) | 471(±76) | 476 (±54) | 186(±25) | 162 (±38) | 18.1 (±14) | 18.5 (±3.6) |
| 2 | LLR u/a | 523(±145) | 403 (±63) | 157(±15) | 160 (±14) | 9.4 (±1.3) | 9.4 (±1.5) | 664(±345) | 627 (±90) | 235(±46) | 191 (±53) | 24.7 (±11.1) | 18.3 (±3.2) |
| 3 | Bilat u/a LR, RIR | 569(±163) | 418 (±110) | 239(±73) | 370 (±430) | 13.4 (±3.1) | 14.6 (±3.9) | 597(±117) | 372 (±90) | 226(±90) | 186 (±29) | 20.2 (±7.6) | 17.7 (±1.9) |
| 4 | Bilat lim MR, LR | 409(±84) | 324 (±33) | 214(±91) | 228 (±131) | 9.7 (±2.5) | 9.0 (±1.0) | 446(±118) | 388 (±53) | 220(±119) | 210 (±55) | 14.4 (±5.3) | 17.4 (±1.6) |
| 5 | u/a RMR | 337(±107) | 421 (±54) | 303(±98) | 185 (±26) | 10.6 (±3.4) | 9.6 (±1.0) | 558(±171) | 524 (±65) | 291(±171) | 210 (±109) | 21.3 (±9.5) | 15.5 (±2.8) |
| Mean (±SD) | | 481.17 (±103.4) | 384.2 (±42.8) | 226.2 (±52.6) | 222.0 (±86.9) | 10.1 (±2.2) | 10.1 (±2.6) | 547.2 (±89.8) | 477.4 (±104.5) | 231.6 (±38.0) | 191.8 (±19.9) | 19.7 (±3.8) | 17.3 (±1.2) |
| *sig* | | ***p<0.05**** | | *p>0.05* | | *p>0.05* | | *p>0.05* | | ***p<0.05**** | | *p>0.05* | |

*Table 2. Confirmed MG and control participant saccadic results: Con = healthy control, bilat = bilateral, L = left, R = right, LR = lateral rectus, IR = inferior rectus, deg = degrees, PV = peak velocity, Amp = saccadic amplitude, Lat = saccadic latency, * - statistically significant.*

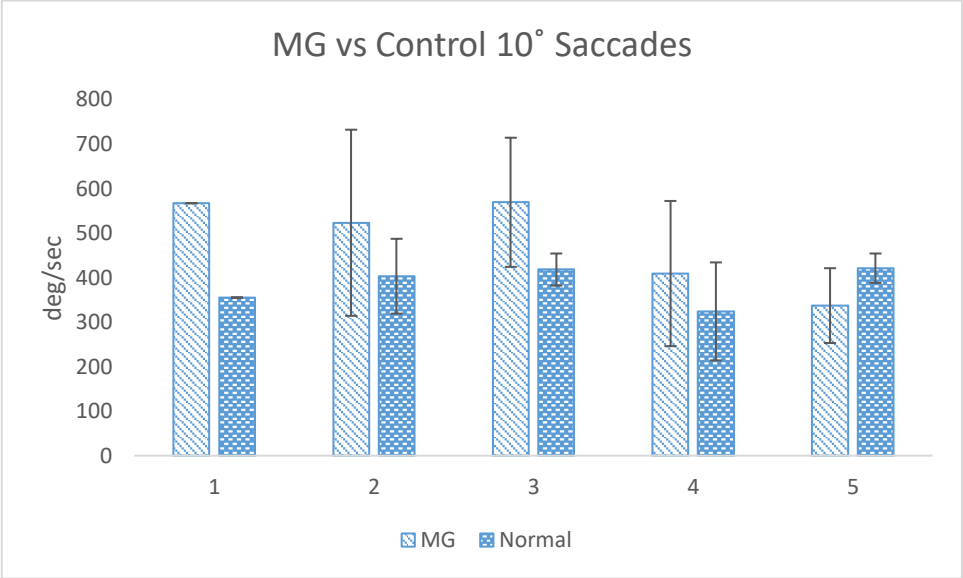



*Figure 1. Mean peak velocity for MG participants vs aged matched healthy controls in 10° saccadic task, error bars = ±SD.*

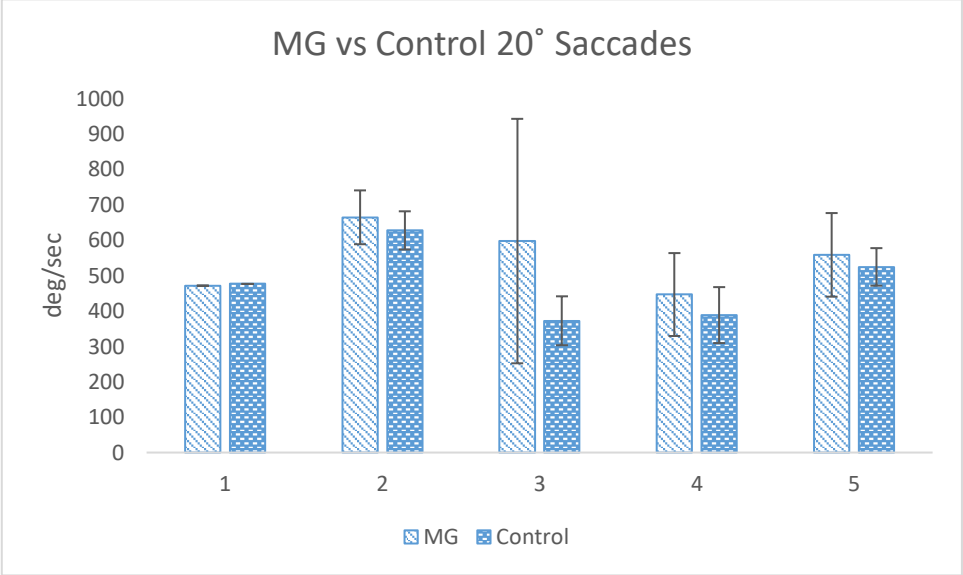
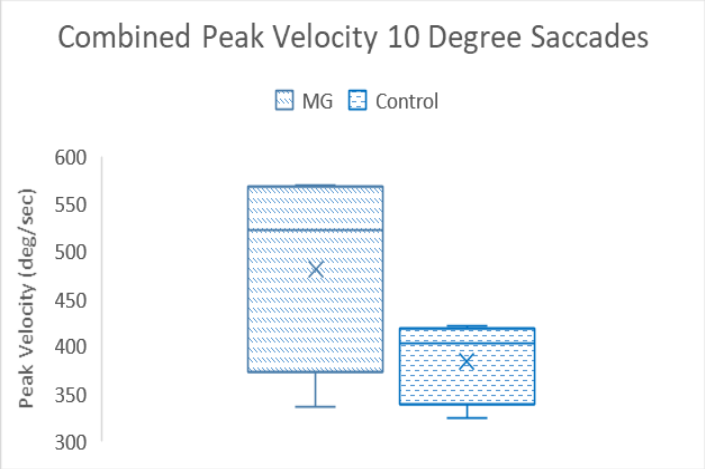



*Figure 2. Mean peak velocity for MG participants vs aged matched healthy controls in 20° saccadic task error bars = ±SD.*



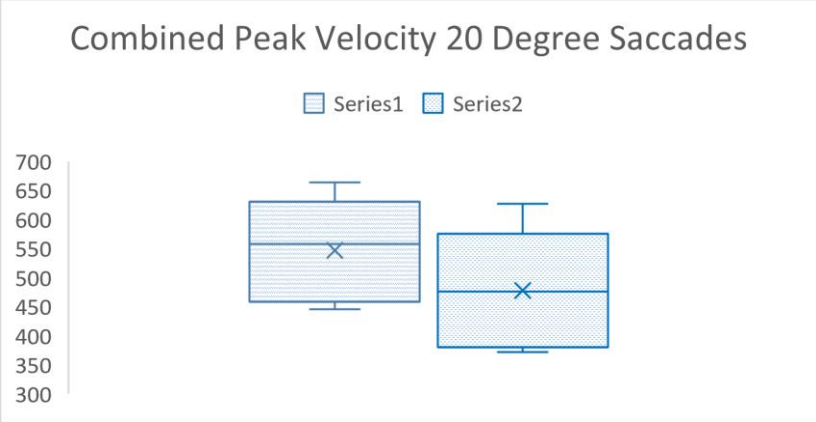




*Figure 3. A. Combined PV for 10° saccades. B. Combined PV for 20° saccades 'X' indicates mean PV for whole group.*

*Saccadic Latency*

Mean saccadic latency for 10° saccades were comparable in both MG and control groups (226.2 ±52.6, 222.0 ±86.9; $p>0.05$) but was significantly longer in MG for 20° saccades (231.6 ±38, 191.8 ±19.9; $p<0.05$).

*Saccadic Amplitude*

There was no hypometria or hypermetria demonstrated in mean amplitude for the MG group at 10° (10.1±2.2) or 20° (19.7 ±3.8) testing and there was no difference in saccadic amplitude between MG and control groups in either 10° (10.1±2.2, 10.6±2.6; $p>0.05$) or 20° saccades (19.7±3.8, 17.3±1.2;

p>0.05). There was some hypometria of 20° saccades in the healthy control group (17.3 ±1.2) but this was not significantly different from the amplitude of MG subjects for that saccade size (p>0.05).

**Discussion**

*Peak Velocity*

All MG participants in this cohort, had smooth pursuit deficits that ranged from mild underactions to mild/moderate limitations of horizontal movement. In both 10° and 20° saccades however, saccadic PV was greater in the MG group compared with the control group (table 1, figure 3). This difference reached statistical significance in 10° ($p<0.05$) testing but failed to reach significance in the 20° saccades ($p>0.05$) which is likely as a result of the small sample size of the cohort in this pilot study. Mean PV was also compared with 'normal' velocity as described by the M-sequence for 10° and 20° saccades[20]. Again, mean PV was significantly greater for both 10° and 20° saccades in MG participants when compared with these values. These results reflect findings in earlier studies[21] which reported paradoxical normal peak velocity in 20° and 40° amplitude saccades in MG patients in the presence of extensive ophthalmoplegia (380°-630°/sec, mean 454°/sec). A subsequent study also reported[23] a statistically significant difference in peak velocity for 10°, 20° and 30° saccades between MG patients (435°± 50° /sec) and patients with other motility defects as a results of other neurological aetiologies (170°/-380°/sec, mean 218°/sec).

Increased synaptic folding in the fibres responsible for saccade generation compared to those responsible for smooth movement is thought to be the reason for this apparent paradox.[24, 26] The availability of AChR sites is therefore more readily diminished by the presence of acetyl choline antibodies making smooth movement more susceptible to the effects of MG.

There is variability displayed within PV performance within this cohort as highlighted in the standard deviations displayed in table 1, and in figures 1 and 2 for individual patients. There was no statistically significant difference in variability between 10° and 20° saccades within the MG group.

Figure 3 illustrates the combined performance for each group and highlights the difference in variability between the MG and control groups for 10° saccades. Variability of ocular signs and symptoms is expected in MG, and it is often a sign that clinicians will use as a point of differential diagnosis in suspected MG cases. As such variability in the performance of these saccadic tasks may be the reason for this variability for MG participants within this cohort.

The variability within the healthy control is more unexpected than for the MG groups with a significant difference in variability between mean PV for 10° and 20° saccades. This seems to be driven by the relatively slower PV of participants three and four who appeared to have slower 20° saccades in comparison to the rest of the healthy group but also relative to their PV performance for 10° saccades. The small sample may be contributing to the variability being detected and repeat testing on a larger sample size may reduce the variability within the data. Nevertheless, regardless of the variability, the data from this cohort shows that the trait of MG patients producing normal or hyperfast saccades compared with healthy controls or the M-sequence in the presence of underactions or limitations of the extraocular muscles is demonstrable using portable, clinically viable testing equipment.

*Saccadic latency*

Normal expected saccadic latency is around 200ms[27] and although the mean latencies for both MG and healthy controls in 10° and 20° saccades exceeded this fractionally and mean latency for healthy controls at 20° was fractionally less, all are still around the 200ms value (table 1). MG participant latency was not significantly different from age matched healthy participants in 10° saccades but was significantly different for 20° saccades. This difference may be driven by individual participants (e.g. MG participant 5) producing latencies that are more than fractionally higher and others producing relatively short latencies (e.g. control 1). Saccadic latency is a measure of reaction time to the new stimulus that is not affected by MG pathophysiology. However, general fatigue associated with MG particularly with the effort to produce slightly larger 20° saccades may offer

some explanation for why there is a difference in latency for these that is not seen in smaller 10° saccades.

A number of other factors such as luminance, type of target and background may also influence measures of latency.[28] Age[27] has also been reported to result in an increase in saccadic latency and given that the mean age of the MG group was 70.8 (±13.6, range 55-91) and 66.0 (±12.8, range 51-85) for the healthy control group; this may provide further explanation for the higher latencies seen in this cohort overall.

*Saccadic Amplitude*

Small amplitude saccades are reported to be hypermetric in MG patients whilst larger saccades are often hypometric.[21, 27] The mean amplitudes in this cohort for the MG group for 10° saccades do not appear to be hypermetric and in fact only one participant (MG participant 3) produced amplitudes that were obviously hypermetric. Mean amplitude for 20° saccades in MG participants was fractionally hypometric, however three out the five MG participants (ID 2, & 4) all produced individual mean amplitudes of 20° or more. There was no significant difference in saccadic amplitude between MG and control groups in either 10° or 20° saccades.

The small sample size is a limitation of this study which the authors recognise. This may well be a contributing factor to the reason why there was a significant difference found between MG and healthy participants for 10° saccades that did not persist for 20° saccades as well as the variability in PV performance. Testing on a larger sample size that includes MG participants, and healthy controls would be useful potentially reducing the amount of variability across the cohort. A comparison of PV performance between MG participants, healthy controls and participants with other neuropathies of the extra ocular muscles would also be interesting. Nevertheless, the result of this study does still demonstrate that the traits reported in earlier lab-based studies which found normal velocity or hyperfast saccades in MG patients with deficits of smooth eye movement can be reproduced using portable equipment in a clinical setting. Furthermore, the Saccadometer does not require the user

to have in depth training in order to be able to use it competently. The saccadic parameters that the equipment measures are recorded by the device and then once connected to the corresponding computer software, all measurements are automatically collated and displayed without the need for the user to undertake any further analysis.

Ocular signs are often the first presenting sign of MG and its differential diagnosis from other neuropathies is challenging. The initial results from this pilot study suggest that, the Saccadmoeter can provide differential diagnosis of MG from other neuropathies which is particularly important in patients where other tests yield inconclusive results. It's simple functionality, portability and ability to identify MG specific characteristics could have a significant positive clinical impact for earlier diagnosis resulting in the administration of appropriate treatment thus improving patient care and quality of life.

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