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Original Article

Quantifying Oculomotor Fatigability for Early Detection of Myasthenia Gravis

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Y. L. Kim, T. T. Nguyen, and S.-B. Hwang have contributed equally in this study.

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Abstract

Objectives:

The aim of this prospective, longitudinal study was to validate video-oculography (VOG) for early detection of myasthenia gravis (MG) in patients with clinical suspicion of MG but lacking confirmatory laboratory results.

Methods:

Thirteen individuals suspected of having MG were studied using a 3-dimensional VOG system. Oculomotor fatigability, defined as the decrement (%) between the second and the last 5 average measures, was calculated.

Results:

Significant reductions in oculomotor ranges were found, exceeding previous cutoff values for horizontal saccades (16.4 ± 9.8%), vertical saccades (18.7 ± 12.6%), horizontal smooth pursuit (15.7 ± 6.0%), and vertical smooth pursuit (27.2 ± 17.4%). Despite initially negative laboratory tests, many participants later tested positive on the neostigmine test (92.3%) and repetitive nerve stimulation tests (69.2%).

Conclusions:

VOG is a reliable diagnostic tool for MG, particularly useful for seronegative patients, allowing for earlier and more accurate diagnosis than conventional methods.

Key Words: myasthenia gravis, early detection, video-oculography, saccade, smooth pursuit, fatigability, oculomotor fatigability

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INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disorder that disrupts neuromuscular transmission, causing muscle weakness characterized by fatigability and fluctuation.[1–6] In ocular MG (oMG), early symptoms such as drooping eyelids (ptosis) and double vision (diplopia) are common, and around 53% of these cases progress to generalized MG (gMG), which can affect muscles involved in speech, swallowing, breathing, and limb movement. The diagnosis of MG relies heavily on clinical evaluation and is supported by various laboratory tests, including the detection of serum autoantibodies, repetitive nerve stimulation (RNS), and the neostigmine test, although these tests have differing levels of sensitivity and specificity.[7,8] Owing to the broad range of MG symptoms and the possibility of negative test results, diagnosing the condition accurately and determining an appropriate treatment strategy can be challenging.

Recent research has indicated that video-oculography (VOG) might serve as a sensitive and specific diagnostic approach for MG.[9] This noninvasive and cost-effective method evaluates oculomotor fatigability by observing the reduction in eye movement ranges following saccadic and smooth pursuit (SP) tasks. The aim of our current research was to verify the dependability of the VOG protocol by applying it to patients who are clinically suspected of having MG but do not have conclusive laboratory findings, such as the presence of serum autoantibodies, RNS, or a positive neostigmine test. These participants were monitored using these confirmatory tests over a period of at least 6 months.

METHODS

Subjects

This study included patients with clinical suspicion of MG who sought medical

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attention at Jeonbuk National University Hospital between June 2019 and May 2022. Initial evaluations consisted of clinical history, neurological examination, and both bedside and laboratory tests. Patients were included if they were clinically suspected of having MG but had negative results in serum autoantibody tests for anti-acetylcholine receptor antibody (anti-AChR) and anti–muscle-specific kinase (anti-MuSK) antibodies, RNS, or the neostigmine test (Fig. 1). Exclusion criteria included any positive laboratory test confirming MG (n = 24), symptoms more accurately attributed to other diseases (n = 15), lack of willingness to participate, or loss to follow-up before 6 months (n = 4). In addition, 1 patient who tested negative on confirmatory laboratory tests within a year, suspected of having a variant of Miller–Fisher syndrome, was excluded. Ultimately, 13 individuals were included in the study (mean age: 54.9 ± 15.4 years; age range: 23–81 years; 6 female patients) (Fig. 1 and Table 1).

Of these, 11 cases were classified as oMG and 2 as gMG based solely on clinical findings. Patients with oMG exhibited fluctuating and easily fatigable ptosis or diplopia, while patients with gMG showed symptoms such as dysarthria, dysphagia, limb weakness, and respiratory difficulty. Despite negative results on laboratory tests—including serum autoantibody tests for anti-AChR and anti-MuSK, RNS, and the neostigmine test—most patients showed positive results on supportive clinical evaluations, such as the forced upward gaze and ice cube tests (Table 1). Oculomotor fatigability was measured using VOG during the initial evaluation, and the results were compared with cutoff values from our previous research involving 24 healthy controls and 46 patients with MG diagnosed through positive conventional diagnostic tests.[9]

Standard Protocol Approvals, Registrations, and Patient Consent

All participants gave their informed consent and were compensated financially for their participation. The study adhered to the ethical standards set by the Declaration of Helsinki and received full approval from the Institutional Review Board at Jeonbuk National University Hospital (approval number 2022-04-044-001).

VOG Recordings

Oculomotor recordings were conducted in the morning, generally between 9 and 11 AM, after participants had eaten

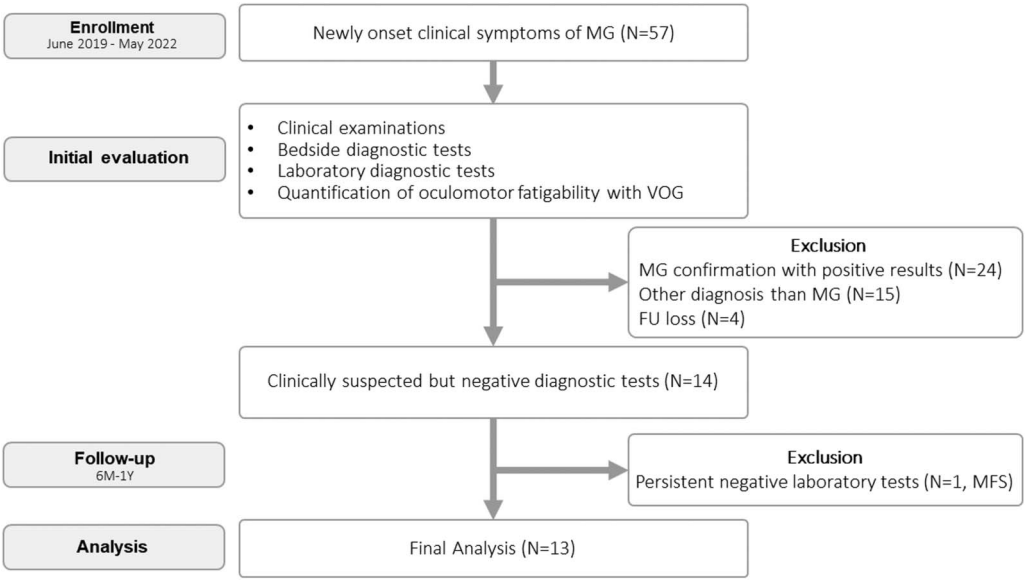

FIGURE 1. Flowchart outlining study selection process. MFS, Miller–Fisher syndrome.

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TABLE 1. Results of Bedside Neuromuscular Examination and Laboratory Diagnostic Tests

				Initial Visit (Y1)																		
					Clinical Symptoms							**Bedside Clinical Test**		**Laboratory Tests**					**Management**			
Patients	**Sex**	**Age**	**Symptom Duration (mo)**	**Ptosis**	**Diplopia**	**Diurnal Fluctuation**	**Fatigability**	**Dysarthria**	**Dysphagia**	**Axial Motor**	**Forced Upward Gaze**	**Ice Cube Test**	**Anti-ach Receptor Ab**	**Anti-MuSK Ab**	**RNS**	**Neostigmine Test**	**MG Subtypes**	**Acetylcholinesterase Inhibitor**	**Steroid**	**Immunosuppressants**
1	F	64	12	+	+	+	+	–	–	–	+	+	–	NA	–	–	oMG	+	–	–
2	M	58	12	–	+	+	+	–	–	–	+	+	–	–	–	–	oMG	+	+	–
3	F	48	48	+	+	+	+	–	–	–	–	+	–	–	–	–	oMG	+	–	+
4	M	40	8	+	+	+	+	+	+	+	+	+	–	NA	–	–	gMG	+	+	+
5	F	56	14	–	+	+	+	–	–	–	–	–	–	NA	–	–	oMG	+	–	–
6	F	23	24	+	+	+	+	–	–	–	–	+	–	NA	–	–	oMG	+	+	–
7	M	73	6	–	+	+	+	–	–	–	+	+	–	NA	–	–	oMG	+	+	+
8	F	51	36	–	+	+	+	–	–	–	–	–	–	–	–	–	oMG	+	–	–
9	M	67	6	+	+	+	+	–	–	–	–	+	–	–	–	–	oMG	+	+	–
10	M	54	12	+	–	+	+	–	–	–	–	–	–	NA	–	–	oMG	+	+	–
11	M	39	16	+	+	+	+	+	+	+	–	+	–	NA	–	–	gMG	+	+	+
12	F	60	24	+	+	+	+	–	–	–	+	+	–	–	–	–	oMG	+	+	–
13	M	81	1	+	+	–	+	–	–	–	–	+	–	NA	–	–	oMG	+	–	–

				Follow-up Visit (Y2)																		
					Clinical Symptoms							**Bedside Clinical Test**		**Laboratory Tests**								
Patients	**Follow-Up Duration (mo)**			**Ptosis**	**Diplopia**	**Diurnal Fluctuation**	**Fatigability**	**Dysarthria**	**Dysphagia**	**Axial Motor**	**Forced Upward Gaze**	**Ice Cube Test**	**Anti-ach Receptor Ab**	**Anti-MuSK Ab**	**RNS**	**Neostigmine Test**	**MG Subtypes**	**Acetylcholinesterase Inhibitor**	**Steroid**	**Immunosuppressants**	
1	12			–	+	+	+	–	–	+	–	+	–	–	+	+	–	NA	+	+	
2	12			–	+	+	+	–	–	–	+	+	–	+	–	–	–	–	–	+	
3	6			+	+	+	–	–	–	–	–	+	–	–	–	+	–	–	+	+	
4	12			+	+	+	+	–	–	+	+	+	–	+	–	+	–	NA	+	+	
5	6			–	+	+	–	–	–	–	–	+	–	–	–	+	–	NA	–	+	
6	10			+	–	+	+	–	–	–	–	+	–	–	–	+	–	NA	+	+	
7	6			–	+	+	+	–	–	–	–	+	–	+	–	+	–	NA	–	+	
8	7			–	+	+	–	+	–	–	–	+	–	+	–	+	–	–	–	+	
9	6			–	+	+	+	–	+	–	–	+	–	–	–	+	–	–	+	+	
10	10			+	–	+	+	–	–	–	–	+	–	–	–	+	–	NA	+	–	
11	6			+	–	+	+	–	–	–	–	+	–	–	–	+	–	NA	+	+	
12	6			–	–	–	–	–	–	–	–	+	–	+	–	+	–	–	+	+	
13	10			–	–	–	–	–	–	–	–	+	–	–	–	+	–	NA	+	+	

Ach, acetylcholine; F, female; M, male; NA, not applicable; +, positive result; –, negative result.

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breakfast to maintain consistent testing conditions. For the majority of participants (11 of 13), the recordings were conducted before they took their daily medication. The other 2 participants were asked to refrain from taking pyridostigmine for 24 hours and corticosteroids for 72 hours before testing. Eye movements were captured using a three-dimensional VOG system (SMI, Teltow, Germany) with a resolution of 0.1 degree and a sampling rate of 60 Hz. The data were analyzed using MATLAB software (version R2022b; MathWorks Inc, Natick, MA), following a method outlined in a prior study.[9] For horizontal and vertical saccades, the targets moved alternately from right (or up) to left (or down) at a frequency of 15 saccades per minute (0.25 Hz) for a duration of 5 minutes, completing 75 cycles. During horizontal SP tasks, the target moved smoothly across the display at a 20 degrees gaze angle for 75 cycles, and during vertical SP tasks, the target moved from top to bottom at a 15 degrees gaze angle. The target's movement followed a predictable sinusoidal path at a speed of 100 degrees/second. To avoid fatigue from repeated trials, participants were given 3-minute rest periods between each trial.[9] The decrements in oculomotor range after repetitive saccades or pursuits were calculated using the following formulas:[9]

$$\text{Decrement of the saccadic range} = 100\% \times \left(1 - \frac{\text{average of the last 5 saccadic ranges}}{\text{the second saccadic range}}\right)$$

$$\text{Decrement of the SP range} = 100\% \times \left(1 - \frac{\text{average of the last 5 smooth} - \text{pursuit ranges}}{\text{the second smooth} - \text{pursuit range}}\right)$$

The primary focus was to compare each estimated decrement with the corresponding cutoff values from a previous study.[9]

Laboratory Diagnostic Tests

Autoantibody Tests

Serum samples were analyzed for anti-AChR antibodies using a standard radioimmunoassay, with results below 0.2 nmol/L deemed negative.[10] For patients who tested negative for anti-AChR antibodies, additional tests were performed for anti-MuSK antibodies using a commercial ELISA kit (IBL International GmbH, Hamburg, Germany).[11]

RNS Test

The RNS test was conducted on the orbicularis oculi, flexor carpi ulnaris, and abductor digiti quinti muscles with the Neuroscreen system (Toennies, Germany) using the belly-tendon technique. The test assessed changes in the amplitude of the compound muscle action potential after 3 Hz supramaximal stimulation, with a decrease of 10% or more between the first and fifth compound muscle action potential considered abnormal.[10]

Neostigmine Test

Improvement in clinical symptoms following the intramuscular injection of 0.5 mg neostigmine is indicative of MG. Owing to limited resources, single-fiber electromyography, which is highly sensitive for diagnosing oMG, was not used in this study.

Data Availability Statement

All deidentified individual participant data that support the findings of this article, including those in the article, tables, and figures, will be made available.

Statistical Analysis

Data were processed and analyzed using MATLAB version 9.13 (R2022b; MathWorks Inc) and SPSS Statistics version 23.0

(IBM Corp, Armonk, NY). The results are expressed as mean ± SD. A one-sample *t* test was used to determine statistical significance, with a significance level set at 0.05 for all tests.

RESULTS

Clinical Characteristics

During the initial visit, diplopia was observed in 92.3% (12/13) of cases and ptosis in 69.2% (9/13), both of which fluctuated and worsened with exercise. Among generalized symptoms, 2 patients (15.4%) exhibited dysarthria, dysphagia, and axial motor impairment, which worsened with repetitive activities or stress and improved with rest. These symptoms had been present for an average of 16.85 ± 7 months before clinical examination. Bedside clinical tests, such as the ice cube test, were positive in most cases with ptosis or diplopia (76.9%, 10/13). The forced upward gaze test, which exacerbated ocular symptoms, was positive in 38.5% (5/13) of cases (Table 1). Despite negative results from laboratory tests, including RNS, neostigmine, and serum autoantibody tests for AChRs and MuSK, patients were treated with acetylcholinesterase inhibitors (pyridostigmine) at an average dosage of 231 ± 32.2 mg (range: 123–360 mg), primarily based on the clinical presentation of fluctuating and fatigable muscle weakness. Bedside examination results, such as the ice cube test and forced upward gaze test, supported this treatment approach (Table 1). In addition, 8 patients were prescribed prednisolone at a mean dosage of 11.3 ± 4.03 mg (range: 5–20 mg), while 4 patients received additional immunosuppressants (2 with tacrolimus, 1 with azathioprine, and 1 with mycophenolate mofetil).

At a follow-up visit, averaging 8.38 ± 4.2 months after the initial treatment, significant clinical improvements were observed. The number of patients with diplopia decreased from 12 (92.3%) to 9 (61.5%) and ptosis decreased from 9 (69.2%) to 5 (38.5%). Fatigability incidence dropped from 100% to 53.8%, and fluctuation decreased from 100% to 84.6%, indicating improvement in MG symptoms with effective management. However, 3 patients with oMG intermittently exhibited systemic symptoms, such as dysarthria, dysphagia, and axial motor weakness, suggesting potential progression to gMG. Follow-up laboratory tests showed that these patients tested positive on either the neostigmine test (92.3%, 12/13) or the RNS test (69.2%, 9/13), while serum antibody tests remained negative (Table 1).

Oculomotor Fatigability Evaluation Using VOG

For the more affected eye, the mean decrement in horizontal saccadic range was 16.4 ± 9.8%, significantly exceeding the suggested cutoff of 7.208% ($P = 0.006$, one-sample *t* test), with 92.3% (12/13) of cases surpassing this threshold (Fig. 2). The average decline in vertical saccadic movement was 18.7 ± 12.6%, also significantly above the cutoff value of 6.401% ($P = 0.004$, one-sample *t* test), with all cases (100%, 13/13) exceeding this limit (Table 2 and Fig. 2). In addition, the mean decrement in horizontal smooth-pursuit range was 13.5 ± 10.2%, significantly exceeding the cutoff value of 9.077% ($P = 0.002$, one-sample *t* test), with 84.6% (11/13) of cases surpassing this threshold. The mean decrement in vertical smooth-pursuit range was 27.2 ± 17.4%, significantly above the cutoff of 6.399% ($P = 0.001$, one-sample *t* test), with all cases (100%, 13/13) exceeding this threshold (Table 2 and Fig. 2).

For the less affected eye, the mean decrement in horizontal saccadic range was 8.6 ± 5.6%, which did not significantly exceed the proposed cutoff of 6.698% ($P = 0.249$, one-sample *t* test), although 53.8% (7/13) of cases did surpass this threshold. The mean decrement in vertical saccadic range was 11.5 ± 10.6%, which also did not significantly exceed the suggested cutoff of 7.264% ($P = 0.174$, one-sample *t* test), though 61.5% (8/13) of cases surpassed it (Table 2). The mean decrement in horizontal smooth-pursuit range was 15.7 ± 6.0%, significantly

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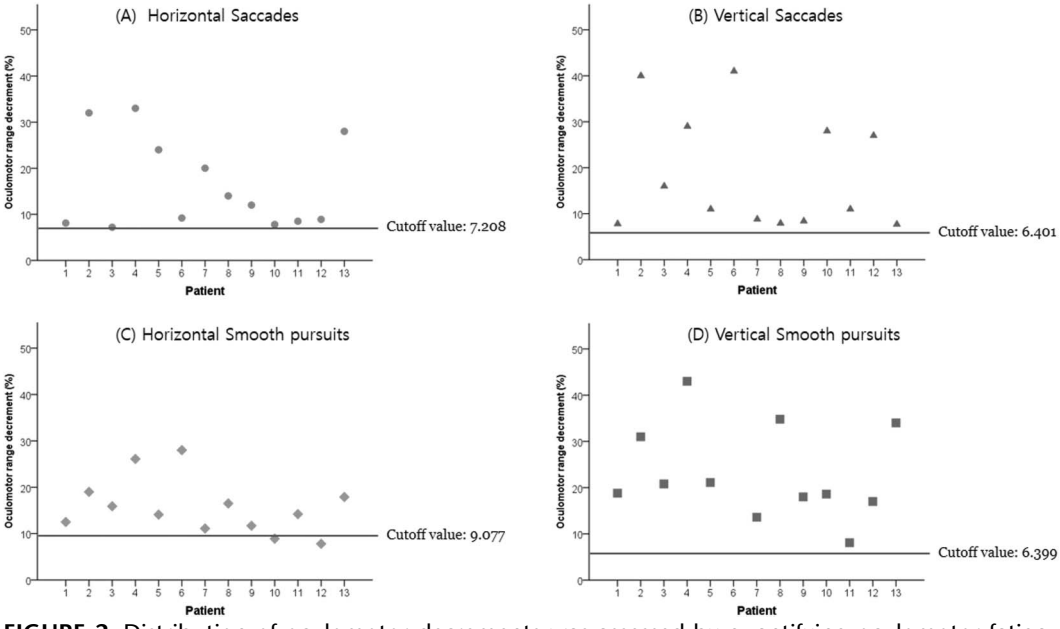

FIGURE 2. Distribution of oculomotor decrements was assessed by quantifying oculomotor fatigability using VOG, depicted as: (A) horizontal saccades, (B) vertical saccades, (C) horizontal smooth pursuits, and (D) vertical SPs. Cutoff values were sourced from the previous data.[9]

exceeding the cutoff of 9.077% ($P = 0.002$, one-sample t test), with 84.6% (11/13) of cases surpassing this threshold. The mean decrement in vertical smooth-pursuit range was 21.3 ± 18.8%, significantly above the cutoff of 6.399% ($P = 0.001$, one-sample t test), with all cases (100%, 13/13) exceeding this threshold (Table 2).

Representative Cases

Patient 1

A 64-year-old woman presented with fluctuating and fatigable bilateral ptosis and binocular vertical diplopia. Vertical diplopia worsened after a forced upward gaze for 2 minutes, and the ice cube test yielded a positive result. Although laboratory tests such as the RNS, neostigmine test, and serum anti-ACh receptor antibody tests yielded negative results, the VOG demonstrated oculomotor fatigability, showing decrements in both horizontal and vertical saccades, as well as in horizontal and vertical SP following repetitive ocular movements. Pyridostigmine (120 mg) was initiated based on suspected oMG. After 1 year, ocular symptoms decreased, but new neck weakness and positive RNS results in orbicularis oculi and abductor digiti minimi muscles and neostigmine tests suggested a progression to gMG (Table 1).

Patient 2

A 58-year-old man with diurnally fluctuating binocular vertical diplopia showed limited supraduction in the OD, worsening with forced upward gaze but improving with rest (Table 1). Ice pack application improved his oculomotor limitation. Although laboratory tests were negative, VOG showed significant fatigability in both saccades and SPs (Fig. 3A and Table 2). Treatment with pyridostigmine (120 mg) and prednisolone (10 mg) led to improvement after 3 months, but symptoms reappeared after voluntary cessation of medication during the 1-year follow-up (Fig. 3B).

Patient 3

A 48-year-old woman with left ptosis and fluctuating vertical diplopia experienced worsening symptoms after discontinuing pyridostigmine for 2 years. VOG indicated oculomotor fatigability despite negative laboratory results (Fig. 3C, 3D and Table 2).

TABLE 2. Analysis of Oculomotor Fatigability of Patients With MG Using VOG at the Initial Visit

	Oculomotor Ranges											
	Saccades, H			Saccades, V			Smooth Pursuit, H			Smooth Pursuit, V		
	Second	The Last Five	Decrement (%)	Second	The Last Five	Decrement (%)	Second	The Last Five	Decrement (%)	Second	The Last Five	Decrement (%)
In the more affected eye												
Pt 1	30.8	28.3	−8.1	30.5	28.1	−7.8	18.4	16.1	−12.5	17	13.8	−18.8
Pt 2	30	20.4	−32	28.1	16.8	−40	18.9	15.3	−19	12.9	8.9	−31
Pt 3	28.6	19.3	−33	32.3	23	−29	20.3	15	−26.1	15.8	9	−43.0
Pt 4	30.4	28.2	−7.2	22.4	18.9	−16	17.6	14.8	−15.9	13.4	10.6	−20.8
Pt 5	30.4	23.1	−24	29.8	26.6	−11	17.7	15.2	14.1	20.4	16.1	−21.1
Pt 6	19.8	18.9	−9.2	19.8	11.6	−41	17.8	12.8	−28.0	12	3	−75
Pt 7	33.6	26.8	−20	22.6	20.6	−8.8	19.8	17.6	−11.1	21.3	18.4	−13.6
Pt 8	21.5	18.5	−14	21.6	19.9	−7.9	13.3	11.1	−16.5	13.5	8.8	−34.8
Pt 9	26.1	23	−12	28.3	25.9	−8.4	18.8	16.6	−11.7	17.3	14.18	−18
Pt10	33.4	30.8	−7.8	18.5	13.4	−28	27.9	25.4	−8.9	18.3	14.9	−18.6
Pt 11	31.6	28.9	−8.5	32.8	28.8	−11	20.4	17.5	−14.2	18.5	17	−8.1
Pt 12	30.3	27.6	−8.9	28.1	20.6	−27	19.2	17.7	−7.8	18.8	15.6	−17
Pt 13	35.5	25.4	−28	27.2	25.1	−7.7	23.9	19.6	−17.9	16.6	10.4	−34
Mean ± SD	29.38 ± 4.5	24.55 ± 4.2	16.36 ± 9.78	26.3 ± 4.7	21.48 ± 5.4	18.74 ± 12.58	19.53 ± 3.4	16.51 ± 3.4	13.5 ± 10.2	16.6 ± 2.9	12.36 ± 4.3	27.21 ± 17.3
In the less affected eye												
Pt 1	30.4	28.7	−5.6	29.8	28	−6.04	18.2	16.3	−10.4	16.1	13.7	−15
Pt 2	31	25.5	−17.7	28.6	24.3	−15.03	19.1	15.6	−18.3	16.8	14	−15
Pt 3	30.3	28.6	−5.6	27.9	27.1	−2.87	17	15.8	−7.06	10.2	9.8	−3.9
Pt 4	29.6	27.5	−7.1	31.8	28.4	−10.69	19.4	15.3	−21.1	15.8	9.2	−42
Pt 5	30.3	25.5	−15.8	30.6	27.9	−8.82	17.8	15.5	12.9	20.1	17.3	−14
Pt 6	19.3	19.1	−1.0	20.8	12.4	−40.38	15.8	14.6	−7.6	13.4	4	−70
Pt 7	34	32.8	−3.5	20.6	20.6	0	19	18.7	−1.58	20.1	18.9	−5.9

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TABLE 2. (*Continued*)

	Oculomotor Ranges											
	Saccades, H			Saccades, V			Smooth Pursuit, H			Smooth Pursuit, V		
	Second	The Last Five	Decrement (%)	Second	The Last Five	Decrement (%)	Second	The Last Five	Decrement (%)	Second	The Last Five	Decrement (%)
Pt 8	21.2	19	−10.4	21.4	19.4	−9.35	12.8	11.3	−11.7	7.9	5.48	−31
Pt 9	26.3	23.6	−10.2	26	24.8	−4.62	19.3	17.1	−11.3	16.2	14.9	−8
Pt10	33.3	32.1	−3.6	18.1	16.2	−10.5	27.7	25.9	−6.5	17.9	15.5	−13
Pt 11	31.2	29.8	−4.49	32.3	28.9	−10.53	20	17	−15	18.5	17	−8
Pt 12	29.5	27	−8.47	27.1	20.4	−24.72	18.3	17.2	−6.01	18.7	15.9	−15
Pt 13	34.8	28.4	−18	27.8	26.1	−6.12	23.2	19.6	−15.5	16.5	10.5	−36
Mean ± SD	29.32 ± 4.5	26.73 ± 4.2	8.57 ± 5.59	26.36 ± 4.6	23.42 ± 5.2	11.51 ± 10.6	19.05 ± 3.5	16.91 ± 3.4	15.67 ± 6.03	16.01 ± 3.6	12.78 ± 4.6	21.29 ± 18.8

H, horizontal; Pt, patient; V, vertical.

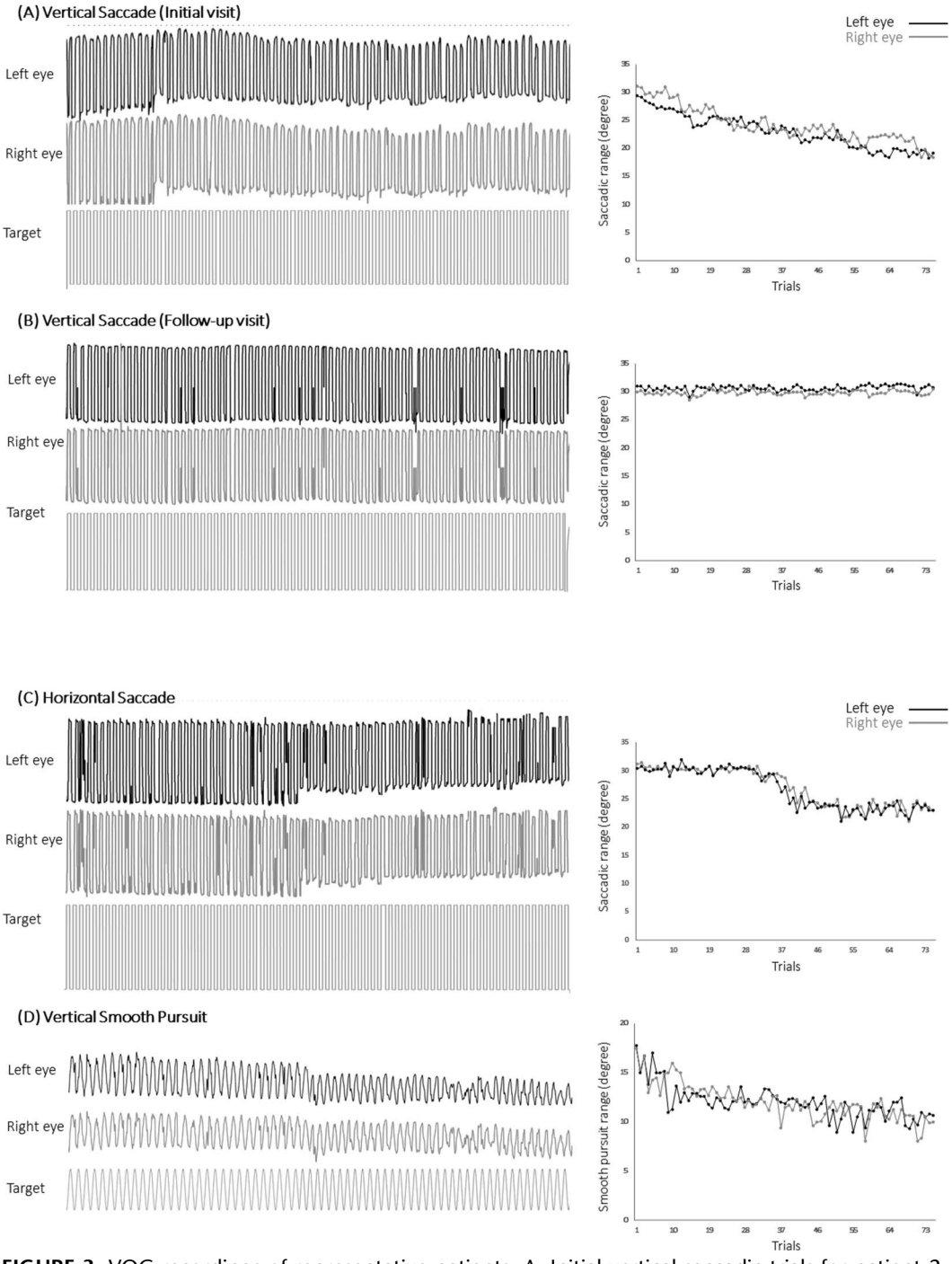

FIGURE 3. VOG recordings of representative patients. A, Initial vertical saccadic trials for patient 2, showing a reduced range in 30 degrees vertical saccades after repetitive movements. B, Follow-up VOG recordings after pyridostigmine and prednisolone treatment, demonstrating no decrement in saccadic range, indicating improved oculomotor fatigability. C, D, Oculomotor fatigability in patient 3, observed through horizontal saccades and vertical SPs. C, Decline in horizontal saccadic range after repetitive 30 degrees horizontal saccades. D, Similar decrement in vertical SP range following 20 degrees vertical movements. These results highlight significant oculomotor fatigability through reductions in both saccadic and SP movements.

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After resuming pyridostigmine (240 mg), her ptosis and diplopia improved at a 6-month follow-up, with RNS and neostigmine tests showing abnormalities.

DISCUSSION

The diagnosis of MG has traditionally relied on the evaluation of clinical symptoms, physical examination findings, and a variety of diagnostic tests. Given the variable sensitivity and specificity of these tests, clinicians frequently depend on a thorough medical history and detailed neurological examinations to establish a diagnosis. To overcome the limitations of traditional diagnostic methods, there has been considerable interest in developing new techniques to measure oculographic abnormalities in MG.[12–17] Recently, attention has turned to using repetitive ocular vestibular-evoked myogenic potentials to evaluate the decreased activity in the extraocular muscles of patients with MG.[18,19] Although this method shows promise with good specificity and sensitivity, its widespread use has been hindered by technical difficulties.

VOG has emerged as a promising diagnostic tool due to its superior accuracy and practicality, although it has not yet been extensively studied or incorporated into clinical guidelines.[20] In this study, we assessed patients exhibiting typical MG characteristics but who initially had negative results on standard diagnostic tests. VOG was able to identify significant oculomotor fatigability, demonstrated by reductions in oculomotor range after repeated trials. Subsequent follow-up visits confirmed the diagnosis of MG, supported by clinical symptoms, response to treatment, and positive results from later laboratory tests. In our recent research, we explored the utility of VOG as a diagnostic tool for MG, focusing on its ability to quantify eye muscle fatigue, which is a hallmark of the disease. We observed a reduction in oculomotor range following repeated saccadic and smooth-pursuit eye movements in patients with confirmed MG. For the more affected eyes, horizontal saccades yielded an area under the curve of 0.863 with a cutoff value of 7.2%, resulting in a sensitivity of 76.1% and a specificity of 100%. Vertical saccades showed an even higher area under the curve of 0.91, with a cutoff of 6.4%, a sensitivity of 78.3%, and a specificity of 95.8%.

In this study, we evaluated the diagnostic utility of these indices in patients who were clinically suspected of having MG, based on typical clinical signs and positive bedside tests, despite initially having negative laboratory results. Notably, these patients exhibited characteristic features of MG, such as improvement with acetylcholinesterase inhibitors or steroid therapy, worsening of symptoms on discontinuation of treatment, and positive RNS or neostigmine tests during follow-up (Table 1). We discovered that in these patients with probable MG, the average decrease in oculomotor range consistently surpassed the cutoff values determined in our previous study for both saccadic and SP movements in the horizontal and vertical planes, even before standard confirmatory tests yielded positive results. These findings suggest that measuring oculomotor fatigability using VOG could serve as a sensitive and specific diagnostic tool for MG, offering precise and noninvasive assessments.

In our analysis, we compared the estimated amplitude reduction of each parameter against the previously established cutoff values for VOG-based assessment of oculomotor fatigability. Significant differences were noted in the more affected eye, particularly in vertical saccades and vertical SP, where all cases (13 of 13) exceeded the specific cutoffs. Horizontal saccades (12 of 13) and horizontal SPs (11 of 13) also demonstrated deviations beyond the threshold (Table 2). A result was considered positive if the amplitude reduction exceeded the cutoff value, indicating MG. When both horizontal and vertical saccadic fatigability tests were positive, the combined sensitivity and specificity were 94.8% and 95.8%, respectively. This suggests that using a combination of indicators

from both saccade directions provides a more reliable diagnostic approach than evaluating them separately.

This study has several limitations. First, our focus was on patients clinically suspected of MG with negative anti-AChR antibodies, RNS test, and neostigmine test, but we did not test for MuSK and LRP4 antibodies in all patients due to resource constraints. This omission may have resulted in missing some cases of seronegative MG, particularly those with MuSK or LRP4 antibodies, thereby limiting the generalizability of our findings. Second, while we assessed the utility of VOG as a noninvasive, quantitative tool for oculomotor fatigability, we did not include confirmatory jitter measurements, which are important for diagnosing MG. The use of VOG in routine practice requires further validation, and its cost-effectiveness compared with established methods such as single-fiber electromyography has not been fully explored. Last, the small sample size may affect the strength and reliability of our findings.

Further research is needed to confirm these findings and to explore VOG's role in facilitating earlier treatment, improving outcomes, and potentially reducing the progression to gMG. Nonetheless, our study underscores the diagnostic potential of VOG in measuring oculomotor fatigability in patients with MG. The results suggest that VOG could serve as a valuable adjunct and an early diagnostic tool, particularly in cases where ancillary tests are negative. While more research is necessary to validate this approach, our findings support its potential to enable earlier intervention and improved therapeutic outcomes, possibly lowering the risk of progression to gMG.

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