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LETTER TO THE EDITORS

Saccadic fatigue as an early indicator for diagnosing myasthenia gravis

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Dear Sirs,

Myasthenia gravis (MG) is the most common disorder affecting neuromuscular transmission, characterized by fatigability and fluctuating muscle weakness that worsens with muscular activity [1, 2]. This autoimmune disorder, which impairs the function of voluntary muscles, predominantly manifests in two forms: ocular MG, affecting solely the eye muscles in about 15% of cases, and generalized MG, impacting multiple muscle groups in approximately 85% of cases [1, 2]. Symptoms often present asymmetrically and typically include muscle weakness, with many patients experiencing ocular symptoms like diplopia (double vision) and ptosis (drooping eyelids) at onset [1].

The diagnostic process for MG involves a combination of clinical evaluations—such as the rest test, sustained upgaze test, ice-pack test, and edrophonium (Tensilon) test—and laboratory tests, including assays for antibodies like anti-acetylcholine receptor (anti-AChR), anti-muscle-specific kinase (anti-MuSK), and anti-low-density lipoprotein receptor-related protein 4 (anti-LRP4), as well as repetitive nerve stimulation (RNS) and single-fiber electromyography (SFEMG) [3–5]. However, the diverse symptomatology, lack of definitive diagnostic criteria in seronegative cases, and the limited sensitivity of some tests present considerable diagnostic challenges [3–6].

Recent advances have introduced video-oculography (VOG) as an innovative, non-invasive, and economical tool for assessing oculomotor fatigability, potentially beneficial for MG diagnosis [7]. The following case describes a young male patient presenting with isolated horizontal binocular diplopia, raising suspicions of MG. Despite negative results from standard diagnostic tests, an in-depth VOG assessment was performed. This involved analyzing repetitive saccadic movements at different frequencies and angles, aiming to uncover any indicators of oculomotor fatigability [8–10].

A 24-year-old male visited our hospital with complaints of intermittent double vision, which he first noticed 6 months ago. This symptom, manifesting one to two times monthly, was particularly pronounced during periods of fatigue or following sustained vertical up-gaze exceeding 20 s. Rest or sleep reliably alleviated the double vision, which notably dissipated upon closure of either eye. He had no history of vision loss, headaches, ocular pain, or head trauma. Ophthalmologic evaluation revealed a right eye visual acuity of 0.2, which improved to 1.2 with corrective lenses, and a left eye visual acuity of 0.1, also improving to 1.2 upon correction. Color vision testing yielded normal results for both eyes. Despite reporting generalized fatigue, the patient exhibited no focal muscular weakness during the neurological examination. Furthermore, no evidence of ptosis, nystagmus, facial paralysis, dysarthria, or sensory deficits was observed. Mild bilateral lateral gaze limitations were noted in both horizontal directions through nine-gaze photography (Fig. 1), yet no signs of Cogan's eyelid twitch, the peek sign indicative of orbicularis oculi weakness, or ptosis following prolonged upgaze were detected. Laboratory tests, including complete blood count, cerebrospinal fluid analysis, thyroid function, anti-ganglioside antibodies including anti-GQ1b,

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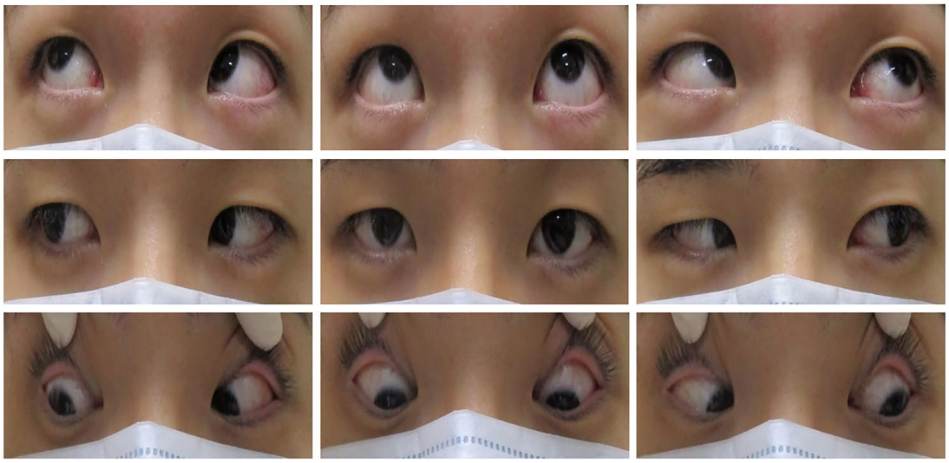

Fig. 1 A nine-gaze photograph of the patient demonstrates slight limitations in lateral gaze in both eyes

immunological assessments, and glucose levels, were all within normal ranges. A brain MRI revealed no abnormalities that could contribute to the diplopia.

In light of the clinical presentation, ocular MG was a primary consideration. Despite this, standard diagnostic procedures including repetitive nerve stimulation (RNS) targeting both the orbicularis oculi and abductor digiti minimi muscles, the edrophonium challenge test, and assays for serum anti-acetylcholine receptor (anti-AChR) and anti-muscle-specific kinase (anti-MuSK) antibodies, failed to confirm the diagnosis, all yielding negative outcomes. Constraints related to our facility's resources precluded the use of single-fiber electromyography (SFEMG). This technique, known for its enhanced sensitivity in diagnosing ocular MG over traditional tests [3, 11], could not be applied.

To further investigate, we employed video-oculography (VOG), an innovative diagnostic tool under evaluation at our institution, aimed at assessing oculomotor fatigue [7]. This involved measuring the reduction in the amplitude of saccadic movements—from the second to the mean of the final five saccades—across varying frequencies. Initially, saccades were elicited at a $\pm 15^{\circ}$ amplitude horizontally and vertically at 0.25 Hz, which did not demonstrate any fatigue-related decline in performance. To deepen our investigation, we then exposed the patient to increased saccadic frequencies (0.5, 0.75, and 1 Hz), incorporating a 3-min rest interval between sessions to minimize the effects of fatigue accumulation. The results at 0.5 Hz did not indicate any significant decrease in saccadic amplitude. Contrarily, the tests conducted at 0.75 Hz and 1 Hz frequencies uncovered a pronounced reduction in the saccadic range, particularly evident at the conclusion of the testing period, with a decrement observed at 45% for the right eye and 46.1% for the left eye at 0.75 Hz, escalating to 53% for the right eye and 55% for the left eye at 1 Hz, as depicted in Fig. 2A–D. Notably, vertical saccadic movements remained unaffected at all tested frequencies, as illustrated in Fig. 2D.

Based on these results, the patient was diagnosed with probable MG and started on Pyridostigmine 60 mg three times daily [5]. Within 2 days of treatment initiation, the patient noted a significant improvement in his symptoms and was subsequently discharged. Over the course of 6 months of follow-up, he reported no recurrence of diplopia. Additionally, a repeat VOG test conducted during a 3-month follow-up visit demonstrated no decrement in the saccadic range at both 0.75 Hz and 1 Hz frequencies, indicating sustained stability in oculomotor function (Fig. 2E).

The current case, characterized by fluctuating and fatigable horizontal binocular diplopia, absence of other explanatory causes for the diplopia, and noticeable symptom improvement following cholinesterase inhibitor therapy, strongly indicated a diagnosis of MG [12, 13]. Despite negative outcomes from both bedside evaluations and standard confirmatory tests, this patient exhibited significant evidence of oculomotor fatigability during horizontal repetitive saccades at relatively high frequencies (0.75 Hz and above).

In our earlier study, we demonstrated that quantifying oculomotor fatigability using VOG could be a sensitive, specific, cost-effective, accurate, and non-invasive diagnostic tool for MG [7]. By identifying saccadic decrements greater than 7.2% for horizontal movements and over 6.4% for vertical movements in the more affected eyes, we were able to distinguish between MG and control groups with high sensitivity (76.1% for horizontal and 78.3% for vertical) and specificity (100% for horizontal and 95.8% for vertical) [7]. This method offers an objective and reproducible approach to measure decrements in oculomotor ranges after repetitive saccadic and pursuit movements, sensitively reflecting the oculomotor fatigue characteristic of MG patients. This study expands on our prior work, which exclusively utilized a 0.25 Hz frequency for oculomotor tests, by incorporating a broader range of stimulation frequencies at 0.5 Hz, 0.75 Hz, and 1 Hz. Specifically, in this case, we noted marked oculomotor fatigability at 1 Hz, evident from the initial saccadic

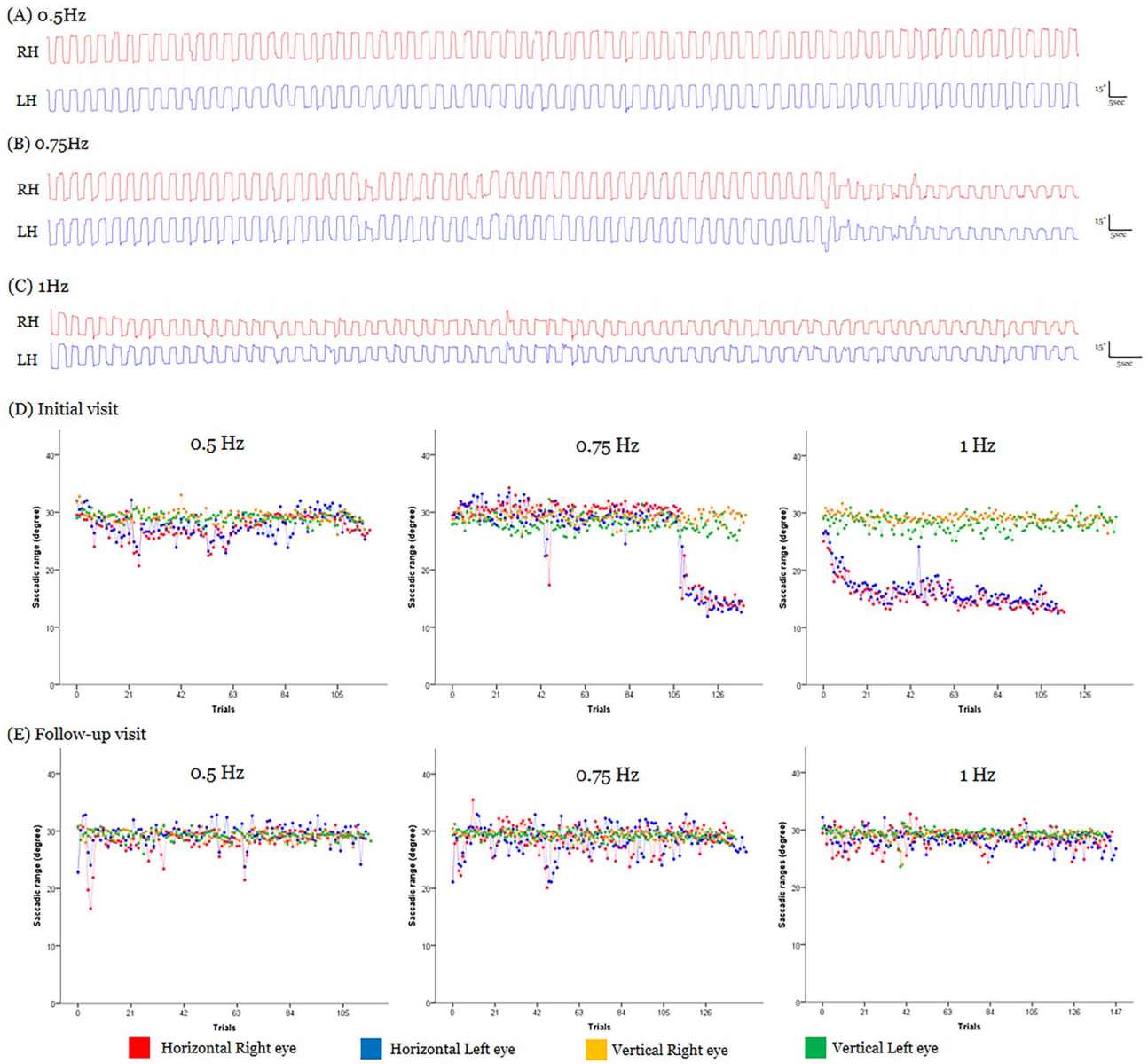

Fig. 2 Saccadic trials were conducted at frequencies of 0.5 Hz, 0.75 Hz, and 1 Hz. During the initial evaluation, video-oculography (VOG) showed no reduction in saccadic range over time for horizontal (right eye: red, left eye: blue) or vertical (right eye: yellow, left eye: green) movements at 0.5 Hz (**A** and **D**). However, a noticeable decrement in the range of horizontal saccades was observed towards the end of the 0.75 Hz trial, and an early decrement was evident at 1 Hz (**B**, **C** and **D**). No significant decrement in range was noted for vertical saccades at 0.75 Hz and 1 Hz (**D**). During a follow-up visit, VOG demonstrated no decrement in range for both horizontal and vertical saccades at 0.75 Hz and 1 Hz (**E**)

cycles. This observation was distinctly different from the delayed appearance of fatigability at 0.75 Hz, and notably, no reduction in the oculomotor range was detected at 0.5 Hz and 0.25 Hz (Fig. 2D). These findings suggest that the ability to detect oculomotor fatigability is likely to increase with the frequency of saccades. This observation suggests that video-oculography (VOG) testing at higher saccade frequencies could enhance diagnostic accuracy and efficiency, and reduce patient discomfort, particularly in early-stage suspected MG cases where conventional tests are inconclusive or not yet positive. However, to determine the optimal saccade frequency for diagnosing MG, further investigation and validation through more comprehensive studies are necessary to substantiate this hypothesis.

The correlation between the frequency of repetitive saccades and the level of observed oculomotor fatigability can theoretically be linked to the safety factor in neuromuscular transmission. This safety factor, crucial in neuromuscular

disorders, represents the ratio of end-plate potential amplitude to the threshold needed for action potential initiation [14–17]. Factors like quantal release, AChR conduction properties, AChR density, and cholinesterase activity collectively contribute to the end-plate potential and the overall safety factor [14, 16, 17]. In MG, repetitive movements decrease neurotransmitter release, diminishing the end-plate potential and, consequently, the safety factor, leading to transmission failure [14, 16, 17]. Theoretically, raising the frequency of repetitive movements pushes the safety margin of neuromuscular transmission to its limits, heightening the onset of muscle fatigue [18].

In summary, this report showcases a young male with clinically suspected ocular MG, characterized by significant oculomotor fatigability evident in VOG assessments at higher frequencies. This underscores the value of VOG in augmenting the diagnostic accuracy for MG, particularly in instances where conventional diagnostic methods yield negative results.

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Author contributions S-YO supervised and contributed to the study concept and revised the manuscript. TTN, JC, and JJK wrote sections of the manuscript. All authors read and approved the submitted version.

Data availability statement The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Declarations

Conflict of interest The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethics statement Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Informed consent Written informed consent was obtained from the patient for the publication of this report and any accompanying images.

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