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CASE REPORT

Late-Onset Ocular Myasthenia Gravis–Like Symptoms During Erenumab Therapy for Chronic Migraine: A Case Report

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Abstract: Chronic migraine (CM) is a disabling neurological disorder for which calcitonin gene-related peptide (CGRP)–targeted monoclonal antibodies, such as erenumab, provide effective prophylaxis. Although generally well tolerated, rare neuromuscular complications resembling ocular myasthenia gravis (MG) have been reported. A 46-year-old woman with CM achieved marked improvement with erenumab for over three years before developing diplopia and intermittent ptosis. Laboratory and imaging studies were unremarkable, but clinical suspicion for MG led to pyridostigmine therapy, resulting in rapid improvement. Brief episodes of dysarthria occurred but resolved within one month. Symptoms disappeared after discontinuation of erenumab and continued pyridostigmine. On re-initiation of erenumab, the patient maintained migraine control without recurrence of MG-like symptoms. This case illustrates a rare, late-onset, reversible MG-like complication of erenumab. Clinicians should remain alert to ocular manifestations even as delayed adverse effects of anti-CGRP therapy.

Keywords: calcitonin gene related peptide receptor, CGRPR, chronic migraine, CM, myasthenia gravis, MG, acetylcholine receptor, AChR:, monoclonal antibody, mAb

Introduction

Chronic migraine (CM) is a highly disabling neurological disorder, defined by headache occurring on 15 or more days per month for more than three months, with migraine features on at least eight of those days.[1] It affects more than one billion individuals worldwide and is associated with substantial functional impairment and reduced quality of life.[1] Conventional preventive therapies, such as topiramate, propranolol, and amitriptyline, are frequently limited by insufficient efficacy and poor tolerability, which often result in suboptimal adherence.[2]

Calcitonin gene-related peptide (CGRP) plays a pivotal role in the pathophysiology of migraine. It contributes to neurogenic inflammation and sensitization within the trigeminovascular system and promotes vasodilation, mast-cell degranulation, and positive feedback mechanisms that amplify nociceptive signaling. Increased CGRP concentrations have been demonstrated during migraine attacks, and inhibition of CGRP signaling has been shown to effectively reduce both the frequency and severity of migraine episodes.[1]

The introduction of CGRP-targeted therapies has represented a major advance in migraine prevention. These include monoclonal antibodies (mAbs) directed against the CGRP ligand (galcanezumab, fremanezumab, and eptinezumab) or the CGRP receptor (erenumab), as well as small-molecule CGRP receptor antagonists ("gepants"), such as rimegepant and atogepant, which are also approved for acute treatment. Randomized controlled trials and meta-analyses have demonstrated their efficacy in both episodic and chronic migraine, and real-world studies support their use in patients with refractory disease.[1] Although CGRP-targeted mAbs are generally well tolerated, post-marketing surveillance has revealed adverse effects beyond headache, including constipation, injection-site reactions, alopecia, fatigue, and throat

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irritation. More recently, Raynaud phenomenon, weight gain, menstrual irregularities, and paraesthesia have also been reported.[3,4] In addition, rare neuromuscular manifestations resembling myasthenia gravis (MG) have emerged, raising questions regarding the physiological role of CGRP at the neuromuscular junction and the potential consequences of sustained CGRP inhibition.[5,6]

MG is an autoimmune disorder of the neuromuscular junction characterized by fluctuating muscle weakness, most commonly mediated by autoantibodies directed against the acetylcholine receptor (AChR) or other associated proteins, such as muscle-specific tyrosine kinase (MuSK) and lipoprotein-related protein 4 (LRP4). In addition to idiopathic and autoimmune forms, drug-induced MG has been increasingly recognized, mainly through mechanisms involving either induction of autoimmunity or direct impairment of neuromuscular transmission.[3] CGRP has a physiological role at the neuromuscular junction, where it modulates acetylcholine (ACh) synthesis and release, regulates AChR expression, and influences synaptic sensitivity. Experimental studies have shown that CGRP enhances neuromuscular transmission, suggesting that pharmacological blockade of CGRP signaling could theoretically compromise acetylcholine-mediated neuromuscular function in susceptible individuals.[7,8]

To date, only a very limited number of case reports have described ocular MG-like manifestations following initiation of CGRP-targeted mAb therapy. These reports remain scarce, and the temporal profile, clinical characteristics, and reversibility of such events are not well defined. Notably, all previously reported cases occurred relatively early after treatment initiation.[5,6]

Against this background, we report a unique case of late-onset ocular MG–like symptoms developing after more than three years of continuous erenumab therapy for CM. This case broadens the emerging safety profile of CGRP-targeted therapies and highlights the importance of continued clinical vigilance for rare neuromuscular adverse effects, even during long-term treatment.

Case Report

A 46 years old female patient came to the ophthalmology clinic with a complaint of double vision. She has been suffering of CM since the age of 15, with almost daily attacks. Initially, her headaches were manageable with caffeine-containing analgesics; however, prolonged use led to severe gastritis. Over the years, she had been intermittently treated with various prophylactic agents, including β-blockers, calcium channel blockers, antiepileptic drugs, and antidepressants. Sumatriptan was prescribed for acute attacks, and she also underwent onabotulinumtoxinA (botox) injections. Her migraine attacks were associated with comorbidities including insulin resistance, hypercholesteremia, overweight and obesity.[9,10] She was on 10mg/day Rosuvastatin to lower bad cholesterol and triglycerides. By the age of 40, her migraine attacks were still considered disabling and poorly controlled.

In mid-2021, she started erenumab injections (anti-CGRP mAb), at a dose of 70 mg every 6 weeks. Migraine attacks frequency and severity were dramatically reduced, with only mild breakthrough attacks between injections. In early 2023, the attacks gradually increased, predominantly stress-induced, and her dose was escalated to 140 mg every 6 weeks, achieving further improvement. In February 2025, the patient started experiencing continuous double vision, especially for distanced objects accompanied by intermittent evening ptosis. She also complained of generalized myalgia but not of any sensory disturbances or urinary and bowel dysfunction. As a mandala artist, she initially attributed her symptoms to fatigue and overwork. After one week, she sought ophthalmologic evaluation. She had bilateral ptosis, mild to moderate in severity with variability in severity during the day. The ptosis became more evident following fatigability testing, indicating a positive fatigue response. The Cogan's lid twitch sign was inconclusive. Diplopia was observed and attributed to a small-angle intermittent esotropia measuring approximately 8 prism diopters. Laboratory workup, including serological testing for MG – anti AChR autoantibodies and thyroid functions, was negative. Chest radiography revealed no evidence of thymoma. Brain and orbital MRI were unremarkable, suggesting migraine-related changes. Nevertheless, MG was clinically suspected.

The patient was prescribed acetylcholinesterase (AChE) inhibitor (pyridostigmine) 3 times a day. Her double vision improved immediately, but 2 weeks later she experienced difficulty of speech, 3 times separated a few days apart, for a few minutes each time. By the end of the first month, symptoms started to disappear markedly. A review of the medical literature identified two previously reported cases of ocular MG-like symptoms associated with prophylactic use of

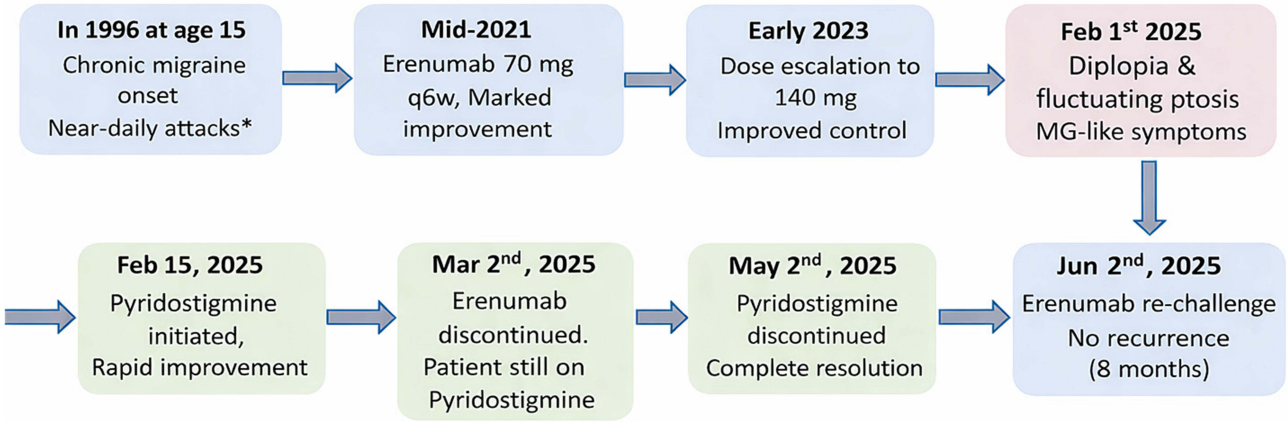

Figure 1 Chronological clinical timeline of erenumab therapy and ocular myasthenia gravis–like symptoms. Light blue-gray: Migraine therapy, Light red-gray: Neuromuscular symptoms, Light green-gray: Symptom resolution. * Patient was intermittently treated with various prophylactic agents, including β-blockers, calcium channel blockers, antiepileptic drugs, and antidepressants.

CGRP pathway mAbs. Hence, erenumab was discontinued. Pyridostigmine was continued for an additional two months until complete resolution of MG-like features.

One month after complete disappearance of MG-like symptoms, because of recurring migraine attacks the patient decided to resume her erunemab injections as her old routine. The time of writing this report, eight months after re-initiation of erenumab, she has remained free of MG-like symptoms, except for myalgia, while achieving sustained migraine control. Figure 1 shows a timeline of clinical and therapy events for the presented case.

Discussion

Two cases of MG-like symptoms developing a few months after the administration of mAbs targeting CGRP signaling have been reported in 2023.[5,6] In addition, 40 diplopia out of 1089 eye adverse drug reactions (ADRs), 58 speech disorders out of 11600 nervous system ADRs, and 589 myalgia cases out of 3466 musculoskeletal disorders associated with erenumab have been reported to the WHO Collaborating Centre for International Drug Monitoring.[11] To our knowledge, this is the first report describing a late-onset presentation of MG-like symtoms, developing after more than three years of continuous erenumab therapy. It is also unique in documenting transient speech difficulty despite ongoing treatment with an AChE inhibitor. Notably, symptoms did not recur when the patient resumed erenumab, suggesting that this adverse effect may be idiosyncratic and potentially reversible.

Many studies dissected the role of CGRP at neuromuscular junctions. Most of these reported that CGRP modulates synaptic transmission mediated by ACh/AChR interaction mostly by enhancement to potentiate muscle contraction.[12] As shown in Figure 2, several mechanisms have been described to explain this role. (1) Through CGRPR, CGRP increases AChR synthesis in vertebrate neuromuscular junctions;[13] (2) this is accompanied with a decrease in AChE, leading to increased sensitivity of the synapse to Ach on an intermediate to long-term basis;[14–16] (3) CGRP enhances Ach release in motor synapses that can be prevented by blocking CGRPR;[17] and (4) CGRP enhances the rapid-decay phase of AChR desensitization.[18–21] Although the first three mechanisms clearly promote muscle contraction, it is not yet known whether enhancement of the rapid-decay phase of AChR desensitization, as described in the fourth mechanism, results in faster recovery of AChRs and consequently resumes and/or augments muscle contraction.

The mechanisms proposed above to explain the development of MG–like symptoms after prolonged use of erenumab as an anti-CGRPR mAb for migraine prophylaxis, remain hypothetical and are not supported by direct clinical or experimental evidence. Nevertheless, these hypotheses are based on a substantial body of in-vitro experimental work, accumulated since 1980s, that specifically investigated the role of CGRP in neuromuscular transmission, mainly in "in-vitro settings".

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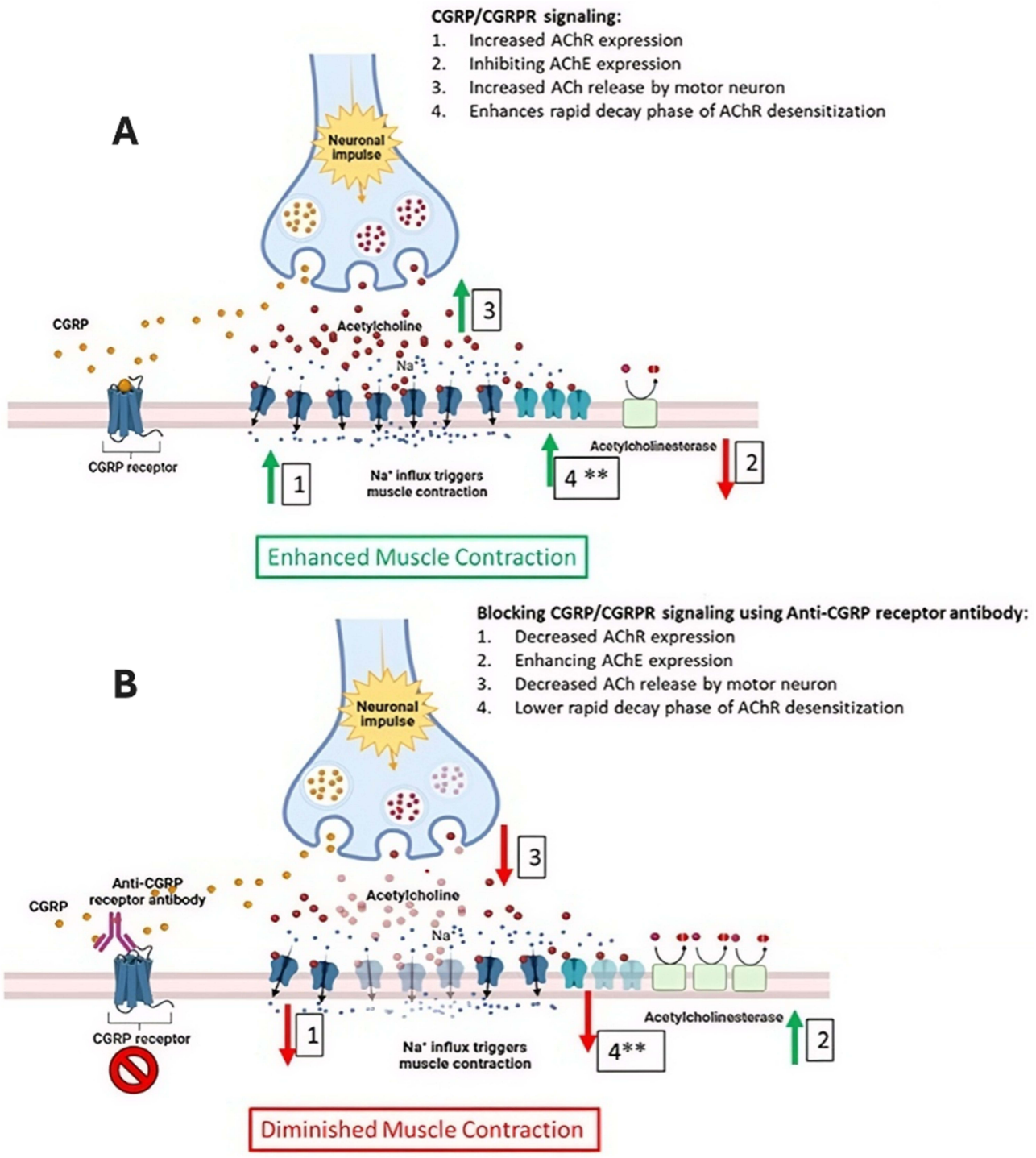

Figure 2 CGRP signaling and neuromuscular transmission at the neuromuscular junction. (**A**) Schematic illustration of the physiological effects of CGRP on neuromuscular transmission, showing enhanced acetylcholine (ACh) release from the motor nerve terminal, increased acetylcholine receptor (AChR) expression, reduced acetylcholinesterase (AChE) activity, and modulation of AChR desensitization kinetics, resulting in augmented sodium (Na^+) influx and enhanced muscle contraction of AChRs and consequently resumes and/or augments muscle contraction. (**B**) Schematic illustration of the proposed effects of pharmacological blockade of CGRP/CGRP receptor signaling by anti-CGRP or anti-CGRP receptor monoclonal antibodies, leading to reduced ACh release, decreased AChR expression, increased AChE activity, and altered AChR desensitization kinetics, with a net reduction in Na^+ influx and weakened neuromuscular transmission. ** It is not yet known whether enhancement of the rapid-decay phase of AChR desensitization, results in faster recovery.

Several important questions remain unresolved, including why such symptoms occur in only a small subset of patients? Why symptom onset was observed within a few months of treatment initiation in the two previously reported cases, whereas symptoms appeared after several years of continuous therapy in our patient? Why the manifestations in our patient, with the exception of myalgia, did not recur after erenumab was reintroduced three months after therapy with AchE inhibitor? And why symptoms started in the eye specifically?

We speculate that these effects may arise in the context of yet-unidentified physiological or pathological conditions, or as a result of specific genetic or epigenetic susceptibility. Interestingly, we came across a recent study by Harlan and Weber (2025) reporting that the presence of the human neonatal Fc receptor (FcRn) may increase the half-life of anti-CGRP or anti-CGRPR mAbs.[22] Because FcRn preferentially binds human IgG, the half-life of therapeutic mAbs increases with the degree of antibody humanization. Erenumab is a fully human IgG2 mAb.[22] Importantly, FcRn expression is known to be upregulated under inflammatory conditions.[23] Therefore, inflammation could prolong the half-life of erenumab, potentially leading to gradual drug accumulation over time. Such accumulation might prolong and/or expand the blockage of CGRP-CGRPR signaling, leading to substantial interference with neuromuscular transmission and contributing to muscle weakness, clinically manifesting as ptosis, diplopia, transient speech difficulty, and generalized myalgia.

From the above-mentioned mechanisms, one can speculate that blocking CGRP/CGRPR signaling might impede ACh driven neuromuscular transmission. In addition to in-vitro experiments, in-vivo studies using appropriate animal models of migraine and anti-CGRP/CGRPR mAbs are needed to further dissect the mechanisms and physiologic settings that potentially cause MG like symptoms. This can eventually help manage prophylactic treatment of CM with such mAbs and with future drug design.

Conclusion

This case report highlights a rare association between erenumab therapy for CM and ocular MG–like symptoms. Clinical improvement with pyridostigmine and resolution after drug discontinuation support a potential causal link. Re-challenge with erenumab did not reproduce symptoms over eight months, suggesting the reaction may be reversible and idiosyncratic. With more people being treated with anti-CGRP mAbs, clinicians should remain alert to diplopia or ptosis in these patients, even as a late-onset complication.

Abbreviations

ACh, Acetylcholine; AChE, Acetylcholinesterase; AChR, Acetylcholine receptor; ADRs, Adverse drug reactions; CGRP, Calcitonin gene-related peptide; CGRPR, Calcitonin gene-related peptide receptor; CM, Chronic migraine; FcRn, Neonatal Fc receptor; IgG, Immunoglobulin G; LRP4, Lipoprotein-related protein 4; mAb(s), Monoclonal antibody(ies); MG, Myasthenia gravis; MRI, Magnetic resonance imaging; MuSK, Muscle-specific tyrosine kinase; WHO, World Health Organization.

Ethics Statement

This study does not require institutional approval for the publication of the case details.

Patient Consent Form

The patient provided written informed consent for the publication of the patient's clinical data.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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