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Refractory generalized myasthenia gravis with myasthenic incomplete ophthalmoplegia successfully treated with eculizumab

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ABSTRACT

Purpose: This is a case of myasthenic incomplete ophthalmoplegia mimicking a partial cranial nerve 3 palsy both subjectively and objectively improving after treatment with eculizumab.
Observations: We chronicle a case of severe generalized myasthenia gravis including myasthenia masquerading as a partial cranial nerve 3 palsy, refractory to pyridostigmine, mycophenolate, prednisone, intravenous immunoglobulin and plasma exchange but responsive to eculizumab.
Conclusions and importance: This case demonstrates ocular and generalized myasthenia gravis refractory to several other therapies but amenable to eculizumab infusions, suggesting this medication may be of significant value in these difficult cases, and should be further explored for refractory ocular myasthenia gravis.

1. Introduction

Myasthenia gravis (MG) is a chronic neuromuscular disease localized to the neuromuscular junction (NMJ) leading to the hallmark symptoms of fluctuating, fatigable weakness of skeletal muscles. MG is often mediated by antibodies (Ab) to the post-synaptic neuromuscular junction components, including nicotinic acetylcholine (ACh) receptors (AChR) and muscle-specific receptor tyrosine kinsase (MuSK). Antibodies to AChR are discovered in about 80% of MG patients. AChR Ab cause dysfunction via binding/blocking receptors, cross-linking and internalization of receptors and activating complement mediated destruction of the end-plate.[1]

50% of MG patients present with isolated ocular symptoms such as diplopia or ptosis, though many progress to develop generalized myasthenia gravis (gMG).[2] Prior retrospective studies have indicated that the risk of MG generalizing is reduced in ocular myasthenia (OM) patients who are treated with immunotherapy (including corticosteroids).[3,4] Progression to gMG can occur at any time, though the risk of generalization is highest within the first two years of symptoms.[5] About 20% of MG patients have only OM, which typically includes upper eyelid ptosis due to levator weakness, eyelid retraction or poor eyelid closure due to orbicularis oculi weakness, and/or diplopia due to deficits in ocular motility that may range from isolated-, multiple or even complete extraocular muscle (EOM) dysfunction. Of note, the pupillary sphincter does not have nicotinic AchRs, so pupils are not affected in MG.[6]

Cholinesterase inhibitors such as pyridostigmine have long been the first-line mainstay treatment for MG.[7] Thymectomy is indicated in thymomatous MG and recent studies have shown the benefit of thymectomy in non-thymomatous AChR Ab + gMG.[8] MG is also treated with a variety of immunotherapies including corticosteroids and other oral immunosuppressants; in more recent years, rapid-acting immunotherapies such as plasma exchange (PLEX) or intravenous immunoglobulins (IVIg) have also been used.[9] Around 10–15% of MG patients have refractory disease, defined as non-responsive to conventional therapies including corticosteroids or multiple steroid-sparing immunosuppressive therapies, intolerable side effects or needing ongoing IVIg or PLEX; refractory patients are more likely to have had an earlier age of onset, have thymomas, demonstrate anti-MuSK antibodies and to be female.[10]

Eculizumab (Soliris, Alexion Pharmaceuticals, Boston, MA, USA) is a recombinant humanized monoclonal antibody that acts as a complement cascade inhibitor via terminal complement protein C5 binding; it inhibits complement protein C5 cleavage into C5a and C5b, thereby preventing C5a-induced chemotaxis and C5b-induced membrane attack complexes (MACs) from forming, sparing the NMJ from complement mediated damage.[11,12] It was FDA approved in 2017 for AChR

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antibody-positive adults with moderate to severe gMG recalcitrant to traditional immunotherapies.[9]

2. Case report

A 71 year old male with medical history including obesity, hypertension, impaired fasting glucose, erectile dysfunction, hypercholesterolemia, insomnia and vitamin D deficiency presented with three days of complete left upper eyelid (LUL) ptosis with diplopia when he manually lifted his LUL. His exam was consistent with a pupil-sparing partial left oculomotor (cranial nerve III, CN3) palsy, including left exo-with hypotropia. His symptoms and labs were not consistent with giant cell arteritis, MRI brain was unremarkable and CT angiography was negative for aneurysmal CN3 compression, leading to the initial diagnosis of an ischemic partial CN3 palsy.

At month 4, alignment and ptosis had slightly improved, but subsequently (month 7) the presumed CN3 palsy did not resolve and was, along with LUL greater than right upper eyelid (RUL) ptosis, clearly fatigable. Ice-pack testing and rest yielded improvement in ptosis (Fig. 1). Ductions were initially full, but fatigued to limited adduction and supraduction. Alignment showed 1 prism diopter (PD) left hypophoria/2 PD exophoria which decompensated to 6 PD left hypotropia/2 PD exotropia with extended cover test. AChR Ab were found to be elevated (binding 11.3 (reference 0–0.4), blocking 40 (reference 0–26) and modulating 45 (reference </ = 45), consistent with myasthenia gravis (MG) with NMJ-related incomplete ophthalmoplegia, or pseudo-CN3 palsy. He did not have a thymoma on chest CT.

By month 9 when he saw neurology, he had notable fatigue and muscle weakness with exertion, and incidences of shortness of breath (SOB) and dysphagia, compatible with gMG. Pyridostigmine 60 mg was started; various doses were trialed for tolerability, but by month 15 he stopped it due to extremity cramping and gastrointestinal side effects unresponsive to propantheline. He declined oral steroids at month 22, electing to remain untreated.

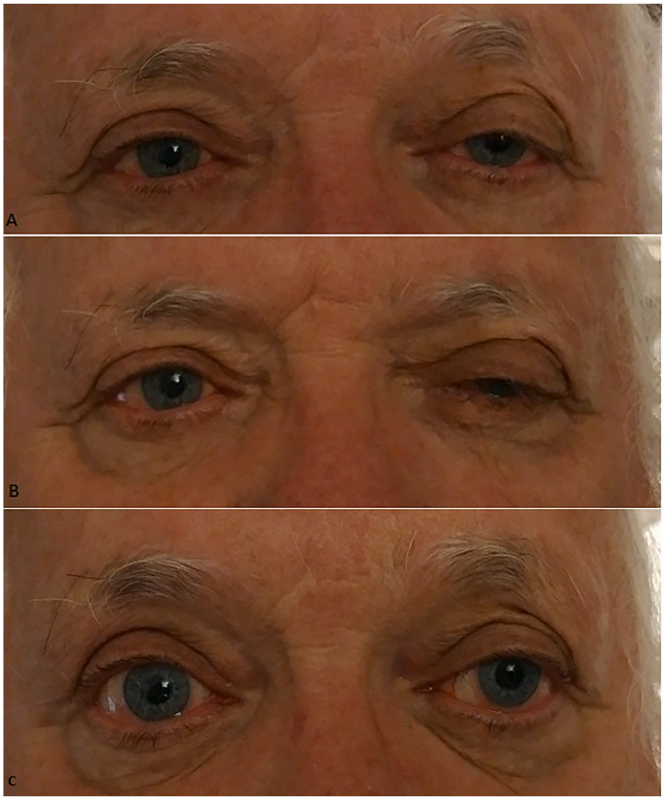

Fig. 1. A Initial bilateral upper eyelid ptosis (left greater than right); B Worsened left upper eyelid ptosis after sustained upgaze; C Improved bilateral upper eyelid ptosis after ice packing then resting.

At month 28, he developed rapidly worsening gMG symptoms and his outside neurologist began prednisone 10 mg daily as an intended bridge to PLEX. Three days later, he developed significant LUL > RUL ptosis, worsened diplopia, difficulty breathing and swallowing. In the Emergency Room, he was in acute neuromuscular respiratory failure so was admitted to the neuro-intensive care unit, where he required intubation and underwent 5 sessions of PLEX. Two weeks later he was discharged on prednisone 60 mg daily, pyridostigmine 60 mg tid, and mycophenolate 500 mg twice daily; diplopia and ptosis were unresolved. Due to persistent symptoms with a Myasthenia Gravis-Activities of Daily Living (MG-ADL) scale of 8, IVIg at 1 g/kg every two weeks was started at month 32.

At month 36, he continued having intermittent difficulty swallowing both liquids and solids, fatigue with chewing, dysarthria, constant SOB even at rest, exertional weakness of arms and legs limiting activities, fatigable ptosis and left pseudo-CN3 palsy with near-constant complete LUL ptosis. He had a second admission (month 38), treated with IVIg, after smoke inhalation lead to neuromuscular respiratory crisis. MG-ADL score was 10 at month 39 and 12 at month 42 with daily bulbar symptoms. His gMG was refractory, so he was vaccinated against meningococcal infection and eculizumab infusions were started in month 44 with a loading dose of 900 mg per week for 4 weeks, then 1200 mg at week 5 and every other week thereafter.

OM and gMG symptoms greatly improved with eculizumab. By month 49, his MG-ADL scale had decreased to 7. At month 58, he only noticed diplopia late in the day, and the LUL was rarely closing with extreme fatigue. He only had a small phoric posture (left hypo-with exophoria), not fatigable to strabismus, and full EOM function (Supplementary Clinic Video). He had 1 mm RUL ptosis, and neither eyelid was fatigable in clinic. His gMG symptoms were significantly improved, as well, with MG-ADL scale of 3 at his most recent clinic visit at month 67 while still on eculizumab. No adverse safety events have arisen in this patient over his 23 months of eculizumab infusions.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.ajoc.2023.101925

3. Discussion

In the 6-month randomized, double-blind, placebo-controlled REGAIN trial (ClinicalTrials.gov, NCT01997229) along with its 3-year open-label extension (NCT02301624), eculizumab was shown to be efficacious in treating refractory AchR antibody-positive gMG patients. While the MG-ADL total score was similar in eculizumab and placebo groups, secondary outcomes such as Quantitative Myasthenia Gravis (QMG), Myasthenia Gravis Quality of Life 15 (MG-QoL15) and Neuro-QOL Fatigue scores were improved in REGAIN at week 26 in patients treated with eculizumab (60.7% vs 41.7% of placebo) or reached minimal manifestations (25% vs 13.3%); in the following open-label study, after 130 weeks of eculizumab, 88% reached improved status and minimal manifestations were achieved in 57.3% of patients.[13] These studies suggest that most patients who respond to eculizumab do so within the first 3–6 months with good probability of sustained positive effects.

While eculizumab has been reported to improve ocular symptoms of MG based on these patient-reported quality of life- and physician-reported muscle group strength questionnaires[14,15] or reductions in severity (mild/moderate/severe ratings) on QMG assessments of ptosis, diplopia and eyelid closure,[15] this is a specific case report of a myasthenic or NMJ-related pseudo-CN3 palsy both subjectively and objectively improving after starting eculizumab.

Al-Haidar et al. have suggested that EOMs are particularly susceptible to dysfunction related to NMJ disorders, citing, among others, their naturally less robust synaptic folding, their very high rate of neuron stimulation, a lower density of AChRs- and lower expression of

complement regulators to protect the postsynaptic cleft from damage compared other muscles, which all put EOMs at higher susceptibility to MG-related complement-mediated damage and dysfunction.[16] This case report demonstrates robust improvement in diplopia and ptosis, with complete resolution of a pseudo-CN3 palsy, along with functionally life-changing improvements in gMG symptoms with complement inhibition.

Eculizumab is currently reserved for only severe refractory gMG. Current consensus on indications for clinical use, including for gMG subgroups who are not AchR-antibody positive or patients who do not meet the REGAIN inclusion criteria, is still debatable[12]; also, its use does carry risk of serious infection (eg meningococcal disease, pneumonia, bacteremia, sepsis, etc[17]), and it involves a significant cost burden (approximately $720,000 per year[18]). Based on early response rates, a treating provider could assess for clinical benefit at 3–6 months, with early discontinuation if there is no demonstrable benefit to mitigate the cost and risks of this medication; however, its efficacy can be impressive in these obstinate cases, and as demonstrated in this case, may be useful in refractory OM, as well.

Patient consent

Written patient consent was obtained, and is available in the patient's electronic medical record.

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Gary Gallagher: Writing-reviewing and editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajoc.2023.101925.

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