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Pediatric Ocular Myasthenia Gravis

Kristen Fisher, DO
Veeral Shah, MD, PhD[*]

Address
[*]Department of Ophthalmology, Texas Children's Hospital, Baylor College of Medicine, 6701 Fannin Street- 5th floor Suite 610.25, Houston, TX, 77478, USA
Email: vee.shah@gmail.com

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Abstract

Purpose of review We present a review of current strategies in the treatment of pediatric ocular myasthenia gravis (OMG). A critical appraisal was performed of the current literature available on OMG and the treatment options available for all age populations. From this data, we present the evidence surrounding therapeutic options for pediatric OMG and discuss treatment outcomes in the pediatric population. We also present gaps in the literature with regard to pediatric OMG and possibilities for future research.

Recent findings While there is data on the use of steroid-sparing immunosuppressive agents for myasthenia gravis (MG), as a whole it is more specific for the use in generalized juvenile myasthenia gravis (JMG) and more focused toward the adult population. In the currently available literature, there have been reports published on the use of steroid-sparing agents including azathioprine, cyclosporine, and mycophenolate mofetil. A recent open-label trial has provided evidence for the use of tacrolimus to improve symptoms of JMG including OMG that were refractory to prednisone. In addition to this, there has been evidence that thymectomy is effective in controlling pediatric OMG and shows a pattern toward preventing generalization of MG, reducing prednisone dosing, and increasing resolution of disease. There are other treatments used in the pediatric population of MG, including intravenous immunoglobulin (IVIG), plasmapheresis, and rituximab, but currently there are no reports on use in OMG.

Summary In the population of patients with pediatric OMG, a high percentage of patients are able to obtain stabilization of symptoms using only pyridostigmine or pyridostigmine in combination with oral prednisone. Rates of generalization of OMG range from 15 to 35%, with higher rates in the adolescent population, but approximately 25% of pediatric patients with OMG can have complete remission. For pediatric OMG patients with ophthalmologic manifestations that are refractory to pyridostigmine and prednisone, the use of steroid-sparing agents has been practiced more recently. In addition to this, thymectomy has been utilized in this population. In both of these instances, no pediatric randomized control trials have been performed to date.

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Introduction

Myasthenia gravis is a B cell–mediated autoimmune neuromuscular disorder where antibodies are directed at acetylcholine receptors (AChR) at the postsynaptic neuromuscular junction, causing weakness or fatigability. Ocular myasthenia gravis (OMG) is a localized form of myasthenia gravis (MG) in which only extraocular muscles, levator palpebrae, and orbicularis oculi are affected, producing symptoms such as ptosis, diplopia, and limitation in extraocular motility, which can in turn cause strabismus and amblyopia. In OMG, typically the weakness has variability through the day, characteristically worsens with repetitive use, and improves with rest, sleep, and cold. Of the annual cases of MG, 10–15% of these are pediatric patients, of which 10–15% are diagnosed with OMG [1, 2]. Most pediatric patients with OMG present with either ptosis and/or strabismus, with exotropia being the most common form of misalignment. Pediatric OMG is more common in prepubertal/preadolescent onset and a high percent of patients being seronegative (especially those that are prepubertal) [2, 3].

Diagnosis

On initial evaluation of a pediatric patient suspected of OMG, one should evaluate the ptosis and strabismus for fatigability and rule out congenital ptosis by history and levator/brow function on clinical exam. Edrophonium or Tensilon (which prevents the breakdown of acetylcholine) testing is the gold standard to diagnosing OMG in adults and a positive test demonstrates immediate improvement of the ptosis and restricted extraocular motility [2]. However, in pediatric patients, it can be technically difficult and the possibility of pharmacologic complications of edrophonium testing, e.g., severe bradycardia and cardiac arrhythmias, make this impractical in the outpatient setting [2]. Alternatively, clinical history, observation, efferent ocular motor exam, and ice-pack, superior gaze, and rest tests are more amenable in making the diagnosis in young children (Fig. 1) [2]. The ptosis typically is intermittent in nature and worse at the end of the day or when the child is fatigued; in advanced cases, the ptosis may be constant. The ptosis can present unilaterally or bilaterally and can at times alternate from side to side. The ocular motor exam measures the ptosis, EOM motility for any restriction, ocular alignment, any overshoot of eyelid twitch when moving the eye from a downgaze to a primary position (Cogan's Lid twitch), and hypermetric saccadic eye movements. Given the autoimmune nature of OMG, an ice-pack test weakens the immune response with 5–10-min placement of an ice-pack on the ptotic eye or the eye with restricted eye movement. On a clinical exam, one can ask a suspected OMG patient to look up superiorly with both eyes for 30 s, and a positive test shows

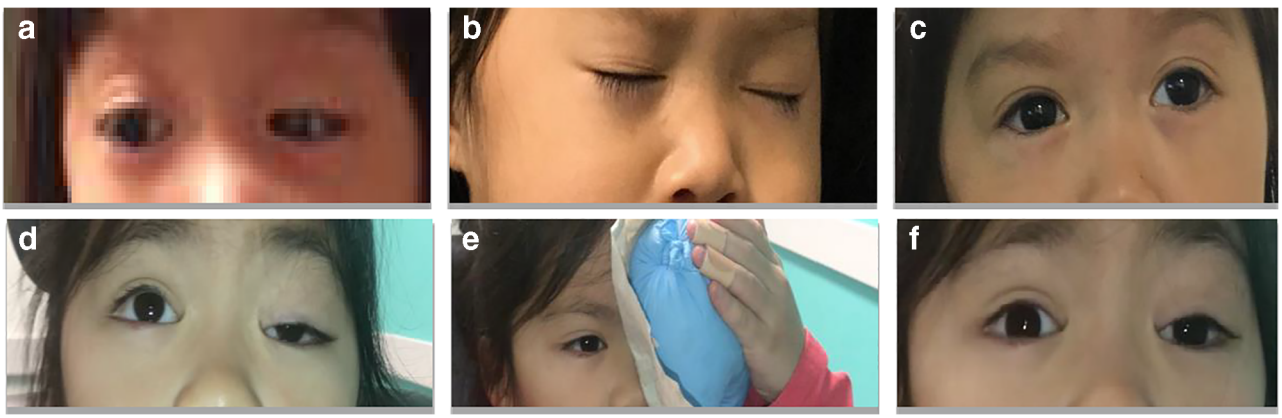

Fig. 1. OMG rest test. **a** Initial presentation with acute left eye ptosis in a 4-year-old girl. **b** Forty-minute pupillary dilation where the patient fell asleep for 30 min. **c** Upon awaking resolution of the fatigue, left levator muscle, and resolution of left ptosis. Ice-pack test. **d** Initial presentation of intermittent left ptosis in a 6-year-old female. **e** Ice-pack place over the affected or symptomatic eye for 5–10 min. **f** Post ice-pack, there is an immediate but transient improvement in the left ptosis (permission has been granted for use of this figure).

fatigability with a breakdown in alignment. With clinical history and exam finding suggestive of OMG, a MG antibody panel can be ordered [2, 4]. Studies have shown that MG antibody testing is seronegative in 30–70% of the pediatric population.

Treatment

Children with exam and history suggestive of pediatric OMG are placed on pyridostigmine trial, which is the first-line treatment. Ocular motility dysfunction is less responsive to pyridostigmine than ptosis, so many patients may continue to have symptoms despite the addition of pyridostigmine [4]. If patients were to continue to have symptoms or have worsening of symptoms, oral steroids are recommended. When symptoms are controlled, weaning the patient to a low dose can be attempted to prevent long-term sequelae of high-dose steroids [5]. If steroids are unable to be weaned, then other steroid-sparing immunosuppressive agents are used. In multiple case series, MG patients have been reported to have received long-term immunosuppressive agents including azathioprine, cyclosporine, mycophenolate mofetil, and tacrolimus [6••]. At this time, a thymectomy should also be considered. A retrospective study involving both adult and pediatric OMG patients who underwent thymectomy has shown effectiveness for OMG, amongst other case series who have shown thymectomy to be ineffective [7]. There has been a correlation in pediatric OMG and B cell–activating factor (BAFF), which may play a role in future directions of treatment. BAFF is a survival factor for B cells, and with an overexpression of BAFF, there is a decrease in B cell apoptosis, which then plays a role in autoimmunity [8]. In patients with pediatric OMG, serum BAFF levels were measured and showed higher pre-immunosuppressive treatment and decreased following treatments [8]. In relation to this, tacrolimus has been recently been trialed for the use as the sole immunosuppressant for pediatric MG, including OMG, as it may reduce BAFF B cells and has shown to improve symptoms in patients refractory to prednisone [9••]. In addition to the pharmacologic management above and for those with refractory symptoms, there are other interventions including prism or occlusion therapy, strabismus surgery (only recommended after stable ocular alignment), or surgical repair of persistent ptosis [10•]. Distinct from adult OMG, especially in the preadolescent pediatric population, there is a decreased rate of generalization of symptoms and a higher rate of resolution of disease. Not only is there a higher rate of resolution of disease in preadolescent but also even without disease resolution there is a high likelihood of stabilization of symptoms with medical management. There have also been patients reported to have received short-course immunomodulating treatments, including plasmapheresis and intravenous immunoglobulin (IVIG). These patients have been shown to be more likely to have generalization of myasthenia and are more commonly of postpubertal/adolescent female [11, 12].

Treatment

Symptomatic Treatment

Pharmacologic treatment

Pyridostigmine

Pyridostigmine, the most commonly used cholinesterase inhibitor, is the first-line treatment for OMG. The action of the medication is meant for symptomatic control and has no effect on the underlying autoimmunity related to OMG. The standard dose of pyridostigmine is 1.0 mg/kg every 4–6 h with a maximum dose of 7 mg/kg/day in divided dosing. The cost of the medication varies depending on dosing and formulation used (liquid vs. tablet), but generally is an inexpensive treatment. Pyridostigmine is contraindicated in those with prior hypersensitivity reaction or those with mechanical intestinal or urinary obstruction. Pyridostigmine can increase

the serum concentration of succinylcholine, causing prolonged neuromuscular blockade, so alternative agents should be considered. The most common side effects reported are nausea, vomiting, abdominal pain, diarrhea, sweating, and cholinergic crisis (severe weakness due to excessive cholinesterase inhibition). One should use caution with increasing the dose to ensure there is no cholinergic crisis, and it is recommended to periodically decrease the dose to ensure the dose is providing the desired effect. In numerous series across both pediatric and adult populations, it has been seen that pyridostigmine alone does not provide optimal improvement for all patients and may not show a significant effect on eye movement abnormalities [4, 13].

Surgical options

Strabismus surgery

In pediatric OMG, strabismus has been reported in rates of up to 76% of patients [14]. Commonly, all preadolescent OMG patients with adequate control of the disease will show stabilization of ocular manifestations, but some subset of patients has residual strabismus and amblyopia [14]. In these populations, once they have achieved stable ocular alignment, the discussion of strabismus surgery can be approached [15]. In one series of patients with pediatric onset OMG who underwent strabismus surgery, 12 patients had horizontal muscle surgery combined with tendon transposition and one with vertical muscle surgery, and five of 13 patients required a second procedure [16]. This study showed that surgical intervention for strabismus should be considered in pediatric OMG patients for whom medical treatment does not improve ocular alignment and symptoms have been stable for at least 6 months [16]. With this procedure, there is a risk for over- or under-correction, requiring an additional procedure [16]. Although patients show improvement with surgical intervention (9 of 13 in above study), one should use caution when proceeding with surgery, because even with stable periods of disease, ocular alignment can continue to change [16].

Surgical correction of ptosis

At times, ptosis related to OMG can be refractory to pyridostigmine, steroids, and other immunosuppressive agents. Due to this, patients have undergone surgical correction of blepharoptosis, including frontalis slings, external levator advancements, and tarsomyectomy with improvement of symptoms [17, 18•, 19•]. Risks include exposure keratopathy, postoperative diplopia, and lagohpthalmos [18•, 19•]. This intervention is more commonly performed on the adult population, and there is no clear guideline on when to intervene [18•]. Some patients will require repeat repair [19•]. It is proposed that a patient's symptoms should be stable for at least 2 years before considering surgical intervention [18•].

Other treatments

Occlusion

Occlusion therapy is used for the management of symptomatic diplopia and amblyopia associated with pediatric OMG. Binocular misalignment due to OMG can be variable and thus cause symptomatic diplopia that can be debilitating in terms of completing daily tasks. Monocular eye patching will resolve binocular diplopia. Amblyopia is a childhood condition in which there is disruption on one or both eyes to connect with the brain resulting in subnormal vision development. Types of occlusion include patching or fogging of a lens [20]. With failure to intervene early on amblyopia, there can be worsening of duction deficits, which may require further intervention in the future and make the amblyopia more difficult to treat [21].

Prisms

Prism glasses can be effective for patients with diplopia refractive to medical treatments [16]. Target angles for prisms are generally made for small-angle deviation noted on primary gaze [16, 22]. The utilization of prisms is primarily for a stable misalignment and disease. Within adequate control, the variability in the disease would need frequent adjustments [20].

Ptosis crutch/eyelid crutch

The eyelid crutch is an inexpensive and noninvasive option for patients with persistent refractory ptosis [20]. The device is a coated pliable wire that is on a frame that is fitted for each patient. When each pair is made, an adjuster fits the device to the patient's desire, helping put the eyelids in the position of comfort. Disadvantages to the device are dry eyes and physical discomfort [20].

Immunosuppression

Oral corticosteroids

Prednisolone

Oral steroids are generally the second-line treatment for OMG and act as long-term immunosuppressants. There are multiple approaches to the initiation of steroids in a patient with OMG. Some start with a high dose, 1–2 mg/kg/day with a max of 60–80 mg, and the dose is then weaned to lowest effective dose given on alternating days [2]. Some patients may develop severe weakness and approximately half will describe mild weakness, so due to this, others will start with a low-dose treatment and titrate to response [2]. Immunosuppressant doses of prednisolone are contraindicated in systemic fungal infections. One will generally notice improvement with steroids around 4 weeks after starting treatment with maximum effect at 3–9 months. Corticosteroids should be used with caution in combination with other immunomodulating medications. Side effects from corticosteroids include growth suppression, hypertension, hyperglycemia,

insomnia, Cushing's syndrome, weight gain, dyspepsia, peptic ulcers, amyotrophy, and others. Prednisolone is an inexpensive treatment option for patients with OMG.

Oral steroid-sparing immunosuppression

Azathioprine

Azathioprine acts on immunomodulation by interfering with T cell function when metabolized to 6-mercaptopurine. Dosing is initiated at 0.5 mg/day and increased in increments of 0.5 mg weekly to a final dose of 1–2.5 mg/kg/day with the maximum benefit being seen between 3 and 12 months after initiation. Azathioprine is contraindicated in pregnancy due to potential for teratogenesis. In patients with rheumatoid arthritis (RA) and a history of treatment with alkylating agents, there is a risk of malignancy. Azathioprine should not be used in combination with other immunosuppressant/immunomodulating medications. The most commonly reported side effects include a flu-like illness, elevations of liver enzymes, leukopenia, and pancytopenia. A randomized, double-blind trial in patients with MG (majority adult patients and not specifically OMG) demonstrated that there are improved outcomes in patients on combined azathioprine and prednisolone, and patients were able to be on reduced doses of prednisolone [2].

Cyclosporine

Cyclosporine is a calcineurin inhibitor that lowers activity of T cell function and has been shown in predominantly adult MG population to improve strength, lower AChR antibody levels, and enable reduction of oral corticosteroid dosing [2]. The standard dosing (adult-based) is initiated at 100 mg twice daily and increase slowly to 3 to 6 mg/kg/day to effect. The onset of effect may take 1 to 3 months with maximum benefit present at approximately 7 months. Cyclosporine use is contraindicated in patients with RA and psoriasis with abnormal renal function, uncontrolled hypertension, or malignancy. It is a CYP3A4 inhibitor and, thus, can interact with many medications that take part in the same pathway. Patients must avoid grapefruit juice as it will decrease metabolism of cyclosporine. Statins should not be used in combination with cyclosporin as the metabolism of statins is impaired. Calcium channel blockers, carvedilol, antifungals, fosphenytoin, phenytoin, and carbamazepine can all affect the serum concentration of cyclosporine and should not be used in combination. Therapy modifications should be considered when multiple immunosuppressive/immunomodulating agents are being used. Dose modifications of dabigatran may be needed as cyclosporine can increase serum concentrations of active metabolites. NSAIDs should be used with caution as they can cause increased nephrotoxic effects, and potassium-sparing diuretics should be avoided as they can enhance the hyperkalemic effects. Side effects reported include headache, hypertension, renal failure, hyperkalemia, leg cramps, tremor, nausea, and dyspepsia.

Mycophenolate mofetil

Mycophenolate mofetil (MMF) is a more novel agent used for immunosuppression for MG, shown to have a low side effect profile, and the therapeutic onset is relatively rapid [2]. MMF blocks purine synthesis and inhibits T cell proliferation [23]. Currently, there is no established dose recommendation for MMF in the pediatric population [24]. Risk of congenital malformations has been reported with use in pregnancy. Common side effects include GI upset, leukopenia, and renal impairment. This can also cause CNS depression, increased risk of infection, reactivation of viral infections, and increased risk of lymphoproliferative disorders. Dosing of MMF and antacids should be separated by at least 2 hours, as there can be reduced effects of MMF. One should take caution with using MMF with other immunomodulating/immunosuppressive agents.

Tacrolimus

Tacrolimus inhibits calcineurin phosphatase which, in turn, inhibits T cell proliferation, playing a role in immunosuppression. It has also been shown to decrease BAFF B cells, which is believed to play a role in pediatric OMG. While no randomized control trials have been performed, there have been emerging studies showing that tacrolimus is effective in the pediatric population for the treatment of OMG and generalized MG. There are no current established dosing recommendations for tacrolimus for OMG, but one case report used dosing of 0.028 mg/kg/day as starting dose and gradually increased over 3–4 weeks with a target monitoring level of 5–6 ng/mL [25]. A maintenance dose of 0.015 mg/kg/day was then used [25]. A maximal effect from the medication was seen in approximately 1–3 months [24]. The most common side effects include tremor, headache, nausea/vomiting, abdominal pain, insomnia, and tingling or swelling in hands or feet. Tacrolimus is a CYP3A4 inhibitor, so patients should avoid grapefruit juice and any other medications affected by this pathway. Caution should be taken when using other immunosuppressive/immunomodulating agents with tacrolimus and also when using antifungal therapies. SSRIs (except trazadone) can decrease the metabolism of tacrolimus, so alternative therapies should be considered.

Surgical treatment

Thymectomy

In adults with MG, especially those with moderate-to-severe disease, thymectomy has been the standard for many years, but there is less data on the procedure in the pediatric population and there are no randomized control trials [24]. In the retrospective studies that have been done on pediatric populations, it has been seen that those who undergo thymectomy have higher rates of remission [24]. Numerous case series have been published looking at thymectomy in pediatric MG [5, 26, 27•, 28, 29••]. In these cohorts, some of these patients had isolated OMG. In a trial with only OMG patients (adult and pediatric), 115 patients who were either unresponsive

to pyridostigmine, were found to have thymoma, or were refractory to immunosuppressive treatment underwent thymectomy. Of these patients, approximately 26% were in remission 12 months following surgery (requiring no medications) and 58% had improvement of symptoms [7]. Most of these studies indicated that thymectomy leads to a lower risk of generalization, improved symptom control, and higher rates of disease resolution. One recent study even showed decreased steroid use following thymectomy [29••]. As current cases have been predominantly retrospective, cohorts have been skewed toward patients with more refractory disease or those with AChR antibodies. A recent review has looked at nonthymomatous OMG and intervention with thymectomy across all ages. It was shown to be an effective treatment, but more multicenter randomized trials will be needed to validate this data [30••]. In the pediatric population, thymectomy is generally safe, with low morbidity and no mortality [29••, 31••]. Increasingly, the procedure is performed via a video-assisted thorascopic technique, which helps decrease hospital admission length. Historically, the procedure was performed via an extended transsternal method, and a significant amount of data is based on this technique [31••]. Another newly used technique is robot-assisted thorascopic surgery [32].

Emerging treatments

The following treatments have more data for use in generalized MG, but may also have a role in OMG, especially in the setting of AChR positivity, although current literature is limited.

Intravenous immunoglobulin

IVIG is used for many autoimmune disorders—neurologic and non-neurologic. In MG, IVIG has been used for short-term acute management in the setting of myasthenic crisis but also has been used as a monthly maintenance immunomodulating treatment. There have been no published reports of IVIG being used for pediatric OMG, only for generalized disease [5, 33]. The most common side effects reported include headache, chills, and hypotension, which generally improve by decreasing infusion rate. Other side effects can include renal insufficiency, aseptic meningitis, muscle cramps, hypersensitivity reaction, and thrombosis. The benefits of IVIG include rapid onset of symptomatic improvement (usually within 1–2 weeks), cost effectiveness over plasmapheresis, and the feasibility to perform than plasmapheresis on young children [24]. For initial dosing or for a myasthenic crisis, dosing can be 1 g/kg/day for 2 days or 0.4 g/kg/day for 5 days with maintenance dosing at 0.4–2 g/kg every 3–6 weeks [24].

Plasmapheresis

In the setting of myasthenic crisis, plasmapheresis is effective for improving strength within days [24]. The mechanism of plasmapheresis is to remove antibodies from circulation, and thus for those patients who are known as AChR positive, is an effective form of rapid treatment. The benefit of therapy generally lasts for 4–10 weeks and may be beneficial as a continued therapy for those who fail to respond to other immunomodulating treatments [2]. The

treatment is often performed as 5 single volume exchanges over a span of 8–10 days [2]. Complications of plasmapheresis include hypotension, sepsis, pneumothorax, and pulmonary embolism [24]. Limiting factors to performing plasmapheresis are access to treatment and cost of service.

Rituximab

Rituximab is a monoclonal antibody directed against CD20 molecule of B cells [23]. Rituximab has been used in adult populations, and few case reports have been made on the use in the pediatric population for MG [34, 35]. Data has shown that rituximab can be effective for patients with refractory MG, such as those who have persistent symptoms despite trials of multiple immunosuppressive agents [36]. There has yet to be any data or reports on the use in isolated OMG. However, according to the published data available, rituximab could be an available option for AChR-positive pediatric OMG patients with refractory symptoms. Rituximab is given at doses of 375 mg/m^2 for 4 weeks as the induction dose. Some patients may not need a follow-up dose, but if needed, follow-up dosing is done at 375 mg/m^2 every 4–10 months [24]. One generally sees maximal effect from the infusion in 1–3 months. Most common side effects include pruritus, headache, dizziness, nausea/vomiting, arrhythmia, and myelosuppression. Rituximab may reduce the effect of live and inactivated vaccines, so infusions should be given at least 2 weeks following vaccination or vaccines should be held until 3 months following rituximab administration.

Eculizumab

Eculizumab is a monoclonal antibody which acts as a complement inhibitor, protecting the neuromuscular junction from complement activation [37]. In 2017, the FDA approved the use of eculizumab for antibody-positive refractory MG [38]. In a double-blind, randomized control trial, adult patients with AChR antibody–positive refractory generalized MG without thymoma were shown to have improvement in strength and more readily able to perform activities of daily living (ADLs) [37]. Patients enrolled in the trial were seen to have benefits after first infusion, and the rate of exacerbation of MG was reduced during the trial period [38]. There has not yet been any data published on the use of eculizumab in the pediatric population, but clinical trials are currently ongoing. Of all the treatments, eculizumab is the most expensive, with costs over $60,000 per month in the USA [38]. The medication is well tolerated and most commonly reported adverse effects include headache, upper respiratory infection, nausea, and diarrhea [37]. In a clinical trial, patients were reported to have meningococcal sepsis; thus, it is recommended for patients to receive *Neisseria meningitidis* vaccine at least 2 weeks prior to infusion if the patient has not already received previously [37]. Currently, there has been no data on the use of eculizumab for OMG.

Conclusion

Pediatric OMG is challenging to diagnose and manage, but the outcomes are generally good with a higher rate of disease resolution. Pediatric patients are also more likely to have stabilization of disease with medical management.

Early treatment has been shown to be optimal and helps prevent generalization to systemic disease. First-line therapy for OMG is commonly pyridostigmine alone or in combination with oral steroids. For patients with refractory symptoms, treatment is generally escalated to a steroid-sparing immunosuppressant. Thymectomy, although no randomized trials have been performed, has been shown to be effective in pediatric OMG, helps decrease rates of generalization of symptoms, improved symptom control, and increase likelihood of symptom resolution. There are also more novel steroid-sparing agents used for MG, including IVIG, plasmapheresis, rituximab, and eculizumab, but no specific data has yet been published on the use of these treatments for strictly pediatric OMG.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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