

“Pediatric Myasthenia Gravis”, as presented  
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## ABSTRACT

Pediatric myasthenia gravis (MG) is a relatively rare, but very treatable condition. Prognosis in pediatric myasthenia gravis is favorable for minimal manifestation status (MMS) or remission when compared to adults.<sup>1</sup> Ocular only presentations are more common, though severe refractory generalized MG presentations also occur.<sup>2</sup> An observational examination is key to the diagnosis and follow-up of pediatric MG patients in the clinic setting.<sup>3</sup> Treatment options are limited by side effect and growth considerations, as well as lack of approved MG medications in the pediatric population. Multidisciplinary care should be considered for pediatric MG, as what is common with other neuromuscular conditions seen in specialty care settings.

**Key words:** pediatric myasthenia gravis, juvenile myasthenia gravis, JMG, pediatric MG

## Introduction

Pediatric myasthenia gravis (MG) is thought of as a rare condition. The estimated incidence of myasthenia gravis (adult and pediatric combined) is 3-30/100,000 cases annually. In children, the incidence is estimated to be 1-5/1,000,000 cases annually.<sup>4</sup> In routine practice, it is important to recognize this treatable condition in the pediatric population. Time to treatment is especially important when MG presents early, as later disability can be prevented with a higher chance of remission of symptoms.<sup>1</sup> If the diagnosis of pediatric MG is recognized early and providers become familiar with this diagnosis, this can spur further referrals to the appropriate teams and specialists.

## Diagnosis and first presentation of pediatric MG: What do you look for in children?

There is a bimodal distribution in the onset of myasthenia gravis, with increased incidence in younger ages, peaking in the second decade of life, and another peak in the

sixth decade of life.<sup>3</sup> Juvenile myasthenia gravis is defined as onset of myasthenia gravis before 18 years of age<sup>5</sup>, though some studies place this cut off at 19 years of age.<sup>6</sup>

JMG age of onset can be as young as 12-24 months, up to an adolescent onset. In a Mayo Clinic cohort study of 364 children, median age of onset for JMG in a population including Lambert Eaton Myasthenic Syndrome (LEMS), JMG, and congenital myasthenic syndrome (CMS), was age 5.1 years.<sup>6</sup> For onset in the pre-pubertal ages, there is a prevalence of more ocular cases<sup>4</sup> and a higher chance of spontaneous remission and minimal manifestation status (MMS) when compared to adults.<sup>1</sup> Ocular manifestations can present initially as alternating ptosis, double vision, or blurred vision only in pre-pubertal children.<sup>7</sup> For post-pubertal MG diagnoses, onset is more likely to be generalized, and can present more like the adult-onset MG. Initial generalized presentations are rare in pre-prepubertal children and interpretation of these symptoms may be more challenging.<sup>8</sup> There is a racial predilection of JMG to the non-white population, which includes Asian, Black, and Hispanic patients, the latter two groups with more refractory cases of generalized myasthenia gravis (gMG).<sup>2,5</sup>

## Presentation of pediatric MG

Many pediatric MG presentations occur with ocular symptoms of asymmetric ptosis and variable ophthalmoplegia,<sup>5</sup> with the main differential diagnoses being congenital myasthenic syndrome (CMS) and transient neonatal myasthenia. Initial presentations of pediatric MG can be in myasthenic crisis with need for inpatient hospitalization in the pediatric intensive care unit (PICU) for intubation needs. The frequency of myasthenic crises in JMG is unknown but accounted for 10% in population-based cohort study of JMG in Norway.<sup>9</sup> More subtle presentations include ptosis that may have gone unnoticed by the family until the ptosis worsens, or a unilateral onset becomes bilateral ptosis. Fluctuation of symptoms may be difficult to ascertain due to the age of the patient.

Chief complaints often include observations specifically regarding fluctuating ptosis or ophthalmoplegia with dysconjugate gaze. This may be an observation by the parent or the teacher. Other parents may note that their child tires more easily than usual with improved energy in the mornings or after a nap. Other times, the patient is referred directly for an evaluation for MG based on an eye examination at the optometrist or ophthalmologist.

For ocular onset in pediatric MG, it is common for the presentation of ptosis to be asymmetric. This can be a unilateral or bilateral onset. If unilateral, ptosis may become bilateral over time. There is often concern for strabismus from optometrists or ophthalmologists if previously evalu-

ated,<sup>10</sup> though this is a fluctuating ophthalmoplegia. Ocular onset can be isolated to the eyes, or present with subtle generalized symptoms.

For generalized onset in pediatric MG, the areas affected can vary on presentation. This can vary from primarily ocular symptoms with very mild proximal limb symptoms, a bulbar presentation, or a true generalized presentation with all areas affected. It is difficult to ascertain and test the fatigability of these areas in clinic based on the age of the patient, so much of the information on disease onset and progression is dependent on parent and other observer history.

### **Pertinent history to obtain in pediatric MG**

The initial evaluation of pediatric MG includes noting the characteristic fluctuation of symptoms. Younger patients present with acute behavioral problems such as more temper tantrums due to fatigue and the inability to express their symptoms. Also, reviewing video and pictures is helpful. Noting symptoms before and after school, or during homework time in the evenings is helpful. Status in the mornings vs. afternoons and status after naps with regards to symptoms are helpful. Chewing, swallowing, or vocal quality in the evenings around dinnertime are also important to ascertain. Other instances to ask include how the patient does with physical education (PE) classes if they attend, as well as how the patient does in hot weather vs. cold weather.

An autoimmune history must be taken as part of a past medical history evaluation, as pediatric MG often co-occurs with other autoimmune conditions such as diabetes type I, celiac disease, and thyroid disease. Just as important is a careful family history to include autoimmune history, as older family members may have thyroid disease, rheumatoid arthritis, or systemic lupus erythematosus, for example. It is more often to find this history in new diagnoses of pediatric MG, as there is likely a genetic contribution for autoimmune susceptibility.

A careful review of systems can reveal additional information needed, such as vision difficulties such as diplopia, or observation of a new “lazy eye” that was not previously present.<sup>10</sup> There may be report of refusal to walk due to leg or muscle pain, or increased fatigue and desire to rest or sleep.

School and social history can reveal if there has been any impact or change in daily school activities, such as in-person or remote class performance. During the pandemic, the patient’s face on screen may demonstrate ptosis or ophthalmoplegia that is visible to the teacher and parent. PE performance may suffer if more fatigue is present, especially if the child participates in timed physical testing.

Homework may be challenging if there is eye or muscle fatigue.

### **Considerations and workup in pediatric MG:**

There is a broad differential for pediatric MG given the younger age of patients and other conditions with similar presentations. This includes congenital myasthenic syndromes (CMS), which are genetic in etiology and involve dysfunction at the neuromuscular junction.<sup>3</sup> Congenital myopathy can present with facial weakness and fatigable proximal limb weakness, but often does not have a diurnal or fluctuating pattern of weakness. Mitochondrial myopathy and mitochondrial-related conditions can have onset with significant weakness and fatigability. Chromosomal conditions can appear like pediatric MG but may also co-occur in MG. In the author’s clinical practice, there are at least two 22q11 chromosomal abnormality (non-DiGeorge) patients with confirmed co-occurrence of autoimmune MG, presenting similarly with generalized symptoms post-pubertally. Birk-Barel Syndrome (heterozygous KCNK9 mutation on 8q24.3) is considered a chromosomal cause of neuromuscular dysfunction and is treated with Mestinon as part of standard practice. Developmental anomalies can also look like a pediatric MG presentation, such as congenital ptosis or congenital cranial nerve abnormalities (ex. congenital cranial nerve VI palsy, or Duane syndrome).<sup>2</sup>

The workup in pediatric MG, given the broad differential, not only includes autoimmune antibody testing for the binding, blocking, and modulating antibodies to the acetylcholine receptor (AChR) and muscle specific tyrosine kinase (MuSK), but also can include genetic testing for congenital myopathy or congenital myasthenic syndromes. For primarily ocular or bulbar presentations of pediatric MG, magnetic resonance imaging (MRI) of the brain can be considered to rule out cranial nerve abnormalities, perinatal injury, or structural developmental issues. Contrast can be added if there is suspicion for an intracranial autoimmune component; for structural reasons only, the study can be done without contrast.

A broad autoimmune workup can be pursued as directed by family history, to include blood counts, inflammatory markers, and rheumatologic markers as needed. Testing for autoimmunity may be sensitive of an autoimmune process, but not specific. The acetylcholine receptor (AChR) antibody panel would be most specific and helpful in the initial evaluation of patients.

### **Examination techniques in children for pediatric MG:**

Pediatric neurologists often must rely on the observational examination for their patients, and the same applies in the evaluation of a young patient undergoing

evaluation for pediatric MG. General examination of the patient starts when the provider enters the room and even while speaking with the patient's parent or caretaker.

In general examination, often what is observed is spontaneous movement. Is there any antigravity movement of proximal muscles? Is there asymmetry of movement between the upper and lower extremities? Is the child not moving or playing as expected for age?

In the eye examination, using a screen (tablet, phone) or a favorite toy is very useful in maintaining sustained gaze. Fatigable ptosis and ophthalmoplegia can be examined in this manner. Aversion of gaze can indicate fatigue or diplopia.

For the arm examination, overhead movements are important to assess, so reaching for objects such as toys or giving high fives are important to test and observe. For the leg examination, watching the movements in the room (ex. climbing, jumping, rising from the floor) is just as important as attempting formal manual muscle testing. A Gower maneuver can be tested in this population as part of the observational examination.

Examination in older children and adolescents is closer to the adult examination for evaluation of MG. For patients who can cooperate, fatigable examinations are important to distinguish ocular only vs. generalized symptoms, as well as to track treatment progress over time. In addition to sustained upward gaze; arm thrusts, repeated ten times, with testing of shoulder abduction before and after, can be done for arm muscle fatigability, and deep squats, repeated ten times, with testing of hip flexion before and after, can be done to assess leg fatigability.

Examinations can be tracked over time with validated measures such as the Myasthenia Gravis Composite (MGC), the Myasthenia Gravis Activities of Daily Living (MG-ADL), and Myasthenia Gravis Quality of Life (MG-QOL) scores. These have only been validated for the adult population. A pediatric QOL score, the Pediatric Myasthenia - Quality of Life 15 (PM-QOL15) has demonstrated correlation with the MGC in a JMG cohort.<sup>11</sup>

### **Treatment options for pediatric MG**

For management of ocular MG, pyridostigmine treatment alone is a popular and very acceptable treatment for parents facing a new diagnosis in their child. Based on updated consensus guidelines, a trial of low dose steroids in combination with pyridostigmine can be used for more symptom control in ocular pediatric MG.<sup>12</sup>

If the initial onset is generalized, thymectomy should be discussed early.<sup>12</sup> This can even be at the first appointment. Earlier thymectomy may result in reduced medications needs in the future, earlier chance for remission or MMS, and

avoidance of NMJ destruction. In addition to thymectomy, discussion of low-dose steroid initiation should also be had. In pediatric MG treatment, steroid doses are not pushed to high doses as they are in adult MG treatment.

Steroids continue to be mainstay of treatment in pediatric MG, though weight gain, acne, decreased bone density, reduced growth velocity, and behavioral changes are specific considerations in treatment of pediatric MG. These are all undesirable side effects for children, especially adolescents. The dose range to aim for is low relative to typical adult dosing: starting 5 to 10mg daily, titrating to no higher than 20mg daily.

For refractory generalized pediatric MG, there are limited steroid sparing therapy options due to lack of pediatric data for these medications in MG.<sup>13</sup> Azathioprine and mycophenolate mofetil have been used in personal practice, but for adolescent patients only due to lack of safety and efficacy data in younger children. The topic of contraception for steroid sparing agents is a necessary discussion and often parents and patients do not agree to an additional prescription as a requirement of treatment.

It is for this reason that intravenous immune globulin (IVIG) and plasma exchange therapy (PLEX) have been used both as acute and chronic treatments for pediatric MG. Chronic IVIG has become one of the widely used treatment options and is approved for use in pediatric MG.<sup>13</sup>

An advantage of IVIG is that it works quickly, has no immune suppression concern, and is an alternative to the oral chemotherapeutic agents with their specific side effect profiles. Unlike steroid therapy, IVIG is weight neutral, and has no effect on growth or teratogenicity.

During the COVID-19 pandemic, IVIG has become one of the treatments of choice for refractory pediatric gMG. There are home infusion options available. There is no immune compromised state and may confer additional protection against infection.

There are ongoing pediatric clinical trials for complement inhibition agents, interleukin-6 antagonists, and neonatal Fc receptor antagonists. However, these treatments are only available by enrolling in a clinical trial. Refractory pediatric MG patients can receive these newer adult gMG approved agents only on an off-label basis.

### **Thymectomy in pediatric MG**

There have been conflicting recommendations in the past regarding thymectomy in MG in general, and especially for pediatric MG patients. There is a now suggestion for thymectomy in the updated guidelines for juvenile MG patients <18 years of age when no suggestion was previously given.<sup>12</sup> The recommendation, however, is stronger for adult patients >18 years and if a thymoma is present, which is

often not the case in pediatric MG. For pediatric MG, thymic hyperplasia is more commonly seen.

Regarding thymectomy in juvenile MG, cohort studies and case series reports have reported favorable outcomes for improvement in symptoms, remission, with low rate of post-operative complications.<sup>14</sup> Thymectomy is recommended in juvenile MG <1 year from onset, so-called “early thymectomy.”<sup>15</sup> More than 90% of patients treated with early thymectomy had favorable outcomes, while thymectomy in patients aged <10 years should be performed in specialized centers due to difficulty of perioperative management.<sup>16</sup>

In the author’s experience, thymectomy early in the disease course in pediatric MG reduces medication need within 1-2 years after the surgery, hastens and improves the chance for remission or MMS, and results in improved MG-specific scales over time such as the MG-Activities of Daily Living (MG-ADL), and the MG-Quality of Life (MG-QOL). These scales are regularly obtained as part of our clinical practice. Improvements after thymectomy in the adult population as stated have been described for adult MG patients more consistently in the medical literature.<sup>12</sup>

For pediatric MG, there is ongoing work for pediatric-specific validated measures such as the PM-QOL15 to track clinical status longitudinally in this population.<sup>11</sup> Use of the MGC, MG-ADL, and MG-QOL, which are validated only for adults, has been used currently in clinical practice and in ongoing clinical trials in pediatric MG.

### **Prognosis and management in pediatric MG:**

Because there are higher rates of clinical remission or MMS in the pediatric MG population,<sup>1</sup> it is a reasonable goal to aim for minimal or no treatment in the management of pediatric MG. In the author’s experience, weaning off chronic IVIG would involve spacing IVIG dosing from every 4 weeks in 2-week intervals, to every 8-10 weeks then discontinuing infusions. This is in line with protocols used at other institutions, in which frequency of chronic IVIG or SCIG for adult MG patients is done at the clinician’s discretion.<sup>17</sup> Patients can be weaned to very low dose or completely off steroid therapy with only once daily or as needed pyridostigmine treatment. Some patients remain on steroid sparing agents alone, such as mycophenolate mofetil alone with minimal symptoms.

For chronic symptoms or refractory patients, continued treatment escalation, as in adults, can be tailored for each patient. This may mean more frequent IVIG, up to every 2 weeks, higher doses of steroids or steroid sparing agents, or discussion of rituximab therapy or off-label therapy with new FDA approved adult medications (eculizumab, ravulizumab, efgartigimod).

However, also in the pediatric MG population, the contribution of functional neurologic disorder must also be considered. There is incidence of anxiety, depression, and adjustment disorder due to having childhood onset of a chronic medical condition. Functional neurologic symptoms may masquerade as MG symptoms or MG exacerbation symptoms. Examples include functional ptosis (non-fatigable), globus sensation with subjective dysphagia without aspiration, and give-way weakness with generalized non-fluctuating body and mental fatigue.

In summary, goals of care are to have the pediatric MG patient feel normal and equal in their abilities to their similarly aged peers.

### **Multidisciplinary care in pediatric MG:**

Pediatric MG is not a condition treated in isolation only by the neurologist or neuromuscular specialist.

At Children’s Hospital Los Angeles (CHLA), we have a dedicated multidisciplinary team for treatment of pediatric MG, that meets with patients on an annual basis to help with chronic management of pediatric MG. In between, patients are seen in our neuromuscular clinic on average, every 3-6 months depending on clinical status and follow-up needs.

The multidisciplinary care at our institution includes a neuromuscular specialist, (MD or DO), and a neuromuscular nurse care manager (NCM, usually RN level) who coordinates care. Pediatric neuromuscular trained physical therapists and occupational therapists aid in energy conservation techniques and adaptations and recommendations for school and home tasks. A registered dietitian familiar with neuromuscular conditions and consequences of steroid therapy can help with weight management and healthy eating. Lastly, a clinical social worker, familiar with neuromuscular patient needs is part of the clinic to address financial, mental health, and other school and social needs.

The above team can also be found in multidisciplinary muscular dystrophy clinics. This team composition and care coordination is intentional. MG patients have many of the same needs as patients with muscular dystrophy or similar disorders, with exclusion of cardiology and pulmonology evaluation to streamline the clinic.

Based on patient report, this is a very well-liked and valuable clinic, and has resulted in tracking of MG-specific scores (MG-ADL, MG-QOL) and neuromuscular testing such as the 6-minute-walk test (6MWT) and 10-minute walk/run test. While the MG-ADL and MG-QOL are validated only for adults, they are not formally validated for children and adolescents. We still can use these data in the older children who are able to participate or perform partial testing and make note of this across examinations.

A bedside swallow test can substitute for bulbar function items on testing, and a “slurp test” can also be utilized quickly in the clinic setting.<sup>18</sup>

Patient education is done continuously in our clinic, and reputable sources such as the Myasthenia Gravis Foundation of America (MGFA), have been introduced via their website at [myasthenia.org](http://myasthenia.org), as well as informational physical brochures and handouts to inform patients and parents regarding myasthenia basics as well as specifics on medications recommended at visits.

### Summary

Onset of MG in the pediatric population is quite varied, so a careful observational examination is key especially for younger patients who cannot fully cooperate. Thymectomy is recommended early in pediatric MG to improve outcomes such as in reduced medical medication needs and chance for remission of symptoms. Treatment options can be quite limited due to side effect profile of steroids and non-steroidal steroid sparing agents, as well as approval of newer agents limited to adult gMG patients. IVIG and PLEX are maintenance options for pediatric MG. Multidisciplinary care and social considerations in pediatric MG can be practiced as standard of care and is quite helpful to patients and their caregivers. Overall, the treatment goal in pediatric MG is “to feel normal.”

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