Juvenile Myasthenia Gravis: Three Case Reports and a Literature Review
Paul Gadient, Jeffrey Bolton and Vinay Puri
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What is This?
Juvenile myasthenia gravis is a rare disorder acquired in childhood, representing 10% to 15% of all cases of myasthenia gravis. Like the adult form, it is generally characterized by an autoimmune attack on acetylcholine receptors at the neuromuscular junction. Most patients present with ptosis, diplopia, and fatigability. More advanced cases may also have bulbar problems and limb weakness. Left untreated, the disease may progress to paralysis of the respiratory muscles. Early recognition of this disease helps avoid unnecessary testing, prevent undue parental anxiety, and stop the progression of symptoms. Here, we relate the clinical course and current status of 3 patients with juvenile myasthenia gravis, discuss the disease in general, and review current treatment modalities.

Keywords: juvenile myasthenia gravis; autoimmune disease; neuromuscular disease

Case 1

An 8-year-old boy was referred by his pediatrician to the clinic because of progressive ptosis of the upper left eyelid beginning in early December 1995. The initial ptosis was painless and without any other neurological symptoms. During the first week of January 1996, the patient developed a diplopia in vertical gaze, which continued to worsen. Initial treatment was with antibiotics thinking the cause was infectious. His eyelid continued to close until he was unable to see with that eye. The patient also complained of a mild headache relieved by Tylenol. He denied any nausea, vomiting, or shortness of air. No impairment of balance, mentation, speech, cognition, judgment, or orientation was reported.

He was delivered full term via spontaneous vaginal delivery and stayed in the hospital for 4 days. Jaundice was noted on day 1, and he received phototherapy. Medical history included 3 bouts of pneumonia resulting in 2 hospitalizations. He had no surgical history. The family history of this African American boy included thyroiditis in his maternal grandmother. He was a good student and lived with maternal grandparents, who were his legal guardians.

On physical exam, the patient was awake and alert. His speech was clear and fluent. Recent and remote memory were intact. Fundoscopic exam demonstrated sharp disc margins bilaterally. Visual acuity was normal. Of note, there was nearly complete left eyelid ptosis with the left eyelid drooping down nearly to the lower aspect of the limbus. There was no ptosis on the right. Both pupils were 4 mm and reacted briskly to light, both directly and consensually. Ocular motility appeared to be full in the right eye. He complained of diplopia on extreme right and left upgaze as well as horizontal medial and lateral gaze. The visual fields appeared to be full to confrontation. Facial strength was full and symmetric with tongue protrusion midline. There was no thyromegaly noted, and sternocleidomastoid and trapezius muscles were intact. Strength, tone, and bulk were all within normal limits. Fine motor coordination was intact, symmetrical, and within normal limits. Deep tendon reflexes were 2+ in both upper and lower extremities. Sensation was intact to light touch, vibration, cold, and joint position. There was no ataxia, dysmetria, or tremor. His gait was normal, including tandem, reverse tandem, skipping, and running.
There were no masses or lesions seen on computed tomography (CT) scan or magnetic resonance imaging (MRI). Complete blood count, sedimentation rate, creatine kinase, serum chemistries, and thyroid levels were unremarkable.

A follow-up visit was arranged a week later for further testing. The patient still demonstrated ptosis. When allowed to rest his eyes for 10 minutes, the ptosis greatly improved (positive rest test). There was also noticeable upward gaze paresis in the left eye with downward gaze intact. A Tensilon test was then preformed, and after the full dose was given, ptosis improved but ocular motility did not. Thus, the Tensilon test was deemed partially positive. Acetylcholine receptor antibody titers, which had been sent to a lab the previous visit, returned with a result of 0.13 (normal < 0.04). With these positive findings, a diagnosis of juvenile myasthenia gravis was established, and the patient was sent home on pyridostigmine 30 mg ter in die.

Three months later the patient was admitted to Kosair Hospital with trouble going up stairs, dizziness, and triplopia. In addition to ptosis and gaze paresis, there was evidence of fatigability in both arms. Prednisone was added to his treatment. Six months after initial presentation, it was noticed that the patient’s thymus seemed enlarged on CT scan. Because of the steroids he was becoming cushingoid and was changed to an alternate day regimen. Over the next year, he continued to be symptomatic and experience side effects of the steroids. Two years after initial diagnosis and obtaining informed consent, he underwent a total thymectomy, finding an enlarged thymus (97.5 g). The surgery was without complications, and he was sent home after 3 days. A few months after the surgery, the patient’s grandmother stated that he had a noticeable increase in energy level but still had bilateral ptosis. After a prednisone taper, he was hospitalized for worsening symptoms and given a course of intravenous immunoglobulin G. After discharge, cyclosporine was started along with pyridostigmine. Over the next 2 years, he became fairly stable; he was able to play basketball for his school and maintain an A/B grade average. Because of noncompliance, he was taken off the cyclosporine and remains on pyridostigmine only. Currently, his only symptom is mild ptosis of the right eyelid.

Case 2

A 3-year-old girl, whose eyelids began drooping in August of 1995, presented with horizontal diplopia, right eyelid ptosis, general fatigability, swallowing dysfunction, and hypophonation. She was an A/B student, who enjoyed cheerleading.

The patient was born following a full-term pregnancy and weighed 7 lbs 11 oz. At 18 months of age, she had a severe thumb injury but no other childhood illness. She reached menarche when in the 6th grade and noticed that her symptoms seemed to worsen during menses. There was no significant family history for this Caucasian girl.

On physical exam, her speech was noted to be slurred after continuous talking. She had extracocular weakness on sustained upward gaze and mild-to-moderate weakness of neck flexion and extension. Her deep tendon reflexes were 2+. She had electrodiagnostic response on repetitive stimulation with electromyography (EMG). Lab tests were unremarkable with the exception of her acetylcholine receptor antibody titer, which was 1.5 (normal < 0.7). Computed tomography and MRI were normal. Having positive EMG and acetylcholine receptor antibody results, the diagnosis of juvenile myasthenia was given, and she was started on pyridostigmine.

A month later she developed bulbar weakness and began to choke. She was transported by rescue with bag-mask ventilation and was intubated for 9 days. At the hospital, she received 5 days of intravenous immunoglobulin G and steroids. She was discharged on steroids and pyridostigmine.

Six months after initial presentation, she underwent plasmapheresis in an attempt to ameliorate symptoms and responded well. Still symptomatic a year after initial onset and after hospitalizations for myasthenia gravis crises, she had a repeat CT done that showed evidence of possible ectopic thymic tissue but no signs of thymoma. Two plasma exchanges were done, and she then underwent a complete thymectomy. The removed specimen was found to be thymic hyperplasia. Initially, she did very well after the operation but was soon readmitted to the hospital for a myasthenic crisis and received 5 days of intravenous immunoglobulin G.

Over the next few years of relapsing and remitting symptoms, she was tried on various drug regimes including pyridostigmine, azathioprine, mycophenolate mofetil, cyclosporine, intravenous immunoglobulin G therapy, and another plasmapheresis. She was finally stabilized on cyclosporine, mycophenolate mofetil, and prednisone for almost a year until she started developing mild renal insufficiency secondary to the cyclosporine. This was discontinued, and she has been doing very well, recently graduating from college.

Case 3

A 4-year-old boy was referred by his primary care physician. According to the patient’s parents, his left eyelid had been drooping for 2 weeks prior to presenting in our office. The drooping was least noticeable in the morning and worsened throughout the day, though no diplopia was noted. There were no other complaints. Medical history and family history were unremarkable for this Caucasian boy. There was no thymoma seen on CT. No decrement was noted on repetitive nerves stimulation. Lab tests revealed...
an elevated acetylcholine receptor antibody titer of 1.3 (normal < 0.4), as well as elevated thyroid peroxidase antibodies and thyroglobulin antibodies. Based on the history, physical, and lab findings, the patient was diagnosed with grade I or ocular juvenile myasthenia gravis.

Because of such mild symptoms, the patient received no treatment initially. His parents were informed of potential neuromuscular toxins to avoid and told to call if the symptoms progressed. On follow-up visits at 3 weeks and 5 months, the patient was found to be asymptomatic, except for mild ptosis after tiring days. Today, he remains asymptomatic without treatment.

Background and Epidemiology

Myasthenia gravis is arguably the best-understood and most-studied autoimmune disease. In infants and children, 3 forms of myasthenia gravis exist: juvenile myasthenia gravis (autoimmune), congenital myasthenia gravis, and transient neonatal myasthenia gravis. Although juvenile myasthenia gravis was coined by Teng and Osserman in 1956, it was first recognized by Erb in 1879. The previous cases were all classified as juvenile myasthenia gravis.

Several European studies have looked at the overall prevalence of myasthenia gravis; an Amsterdam study demonstrated a prevalence of 53 per million population, an English study 15 per 100,000, and a Swedish 14 per 100,000. Autoimmune myasthenia gravis presenting in childhood is rare and accounts for about 10% to 15% of myasthenia gravis cases in North America, with an annual incidence of 1.1 per million total population. In Japan and China, early onset is far more frequent with up to 43% presenting by adolescence. There is also a difference seen in the incidence between African Americans and Caucasians, with African American children and adolescents having a higher incidence. These differences point to potential differences in genetic susceptibility and possible environmental involvement. Human lymphocyte antigens (HLA), which play key roles in several autoimmune diseases, have been associated with myasthenia gravis in Caucasian populations. This helps explain the increased incidence of other autoimmune diseases seen in myasthenia patients. The subtypes associated with adult onset myasthenia gravis include HLA-DR3, -A1, -B8, and -DQw2.6 The muscle-specific kinase antibody–positive form of myasthenia gravis, described below, is notable for a greater prevalence among women than among men and is associated with the haplotype HLA-DR14-DQ5.

Etiology

Juvenile myasthenia gravis is an antibody-mediated disease targeting the acetylcholine receptors on the postsynaptic part of the neuromuscular junction. When these antibodies bind to the acetylcholine receptor, the receptor’s degradation is accelerated. By binding to the receptors, antibodies physically block synaptic transmission and induce local deposition of complement. All of these factors result in immune-mediated injury, which disrupts the normal transmission at the neuromuscular junction.

Although acetylcholine receptor antibodies account for about 80% of cases of autoimmune myasthenia gravis, other forms also exist. Up to 70% of acetylcholine receptor antibody–negative cases may be due to autoantibodies against the muscle-specific kinase, MuSK, although most studies suggest lower frequencies. Boneva et al recently reported that muscle-specific kinase antibodies initiate cell cycle arrest, inhibit cell proliferation, and downregulate several genes important to the organization and function of the neuromuscular junction, thereby disrupting neuromuscular transmission and inducing muscle atrophy.

Clinical Features

Most patients with juvenile myasthenia gravis present with fluctuating motor weakness. Symptoms worsen throughout the day and after continuous activity. Extraocular muscles are usually the first affected by the disorder, leading to ptosis, diplopia, and strabismus. Up to 90% of children with the disease will have such symptoms, with ptosis being the most common and most noticeable. Diplopia may not be initially apparent but may be elicited, with the child sustaining an upward gaze. Interestingly, almost 50% of patients will consult an ophthalmologist first, and extraocular involvement remains the only manifestation in almost 15% of children and adolescents. These patients are said to have ocular myasthenia gravis. During the early stages, it may be difficult to distinguish between ocular and general types because they both encompass ocular symptoms. However, if generalized symptoms do not develop within a year of onset, they are unlikely to do so.

Bulbar weakness is also common and can affect up to 75% of patients. Altered chewing and swallowing, drooling, nasal or weak voice, and poor pronunciation are all symptoms of bulbar involvement. Extremities may also be involved, with proximal extremities affected more, manifesting as fatigability when climbing up and down stairs. More serious symptoms include involvement of the diaphragm, which leads to respiratory distress (myasthenic crisis) and the need for immediate respiratory support and hospitalization.

Muscle-specific kinase antibody–positive patients generally have a more severe form of the disease than acetylcholine receptor antibody–positive patients, with more pronounced bulbar and respiratory signs but less limb involvement and less frequent thymic abnormalities. The extensive bulbar involvement is more likely to lead
to wasting of the tongue and facial muscles in these patients.17

Osserman devised a grading scale for myasthenia gravis that is widely used.18

Grade I: Weakness restricted to extraocular muscles.
Grade II: Generalized weakness that is either mild or moderate, sparing respiratory muscles.
Grade III: Acute fulminating disease with early respiratory involvement.
Grade IV: Severe disease with life-threatening respiratory involvement.

Diagnosis

Depending on the level of involvement, a high index of suspicion may be needed to make the diagnosis of juvenile myasthenia gravis. Many patients may have already been seen by their primary care physician or ophthalmologist. A good history and physical exam are often beneficial in making the diagnosis. On exam, weakness and muscle fatigability can often be elicited with simple bedside tests including the lid twitch and ‘ice-bag’ tests.

Apart from history and clinical exam, other tests exist to aid diagnosis. The Tensilon test involves infusing a dose of edrophonium under a controlled setting. Edrophonium is a quick-acting cholinesterase inhibitor, which prevents breakdown of acetylcholine, subsequently increasing the neurotransmitter’s synaptic concentration. The most common protocol begins with the administration of 2 mg, followed by 3 to 8 mg until there is observable improvement or 10 mg have been administered. The patient should be observed for 60 seconds between doses and for 3 to 5 minutes upon completion of the test.

Electrophysiologic testing is another useful diagnostic aid. There is usually a decremental EMG response to repetitive nerve stimulation, where a decrement of greater than 10% is considered a positive result. Single-fiber EMG is a particularly sensitive test for the diagnosis of myasthenia gravis, but it comes at the price of reduced specificity. Therefore, positive results should be followed by traditional EMG and nerve conduction studies. It should be noted that the muscle-specific kinase antibody–positive form is rarely detected by repetitive nerve stimulation, and single-fiber EMG is the preferred electrophysiologic test in these patients.

Lab tests quantifying acetylcholine receptor antibodies can help confirm the diagnosis, with approximately 80% being seropositive. As mentioned previously, many acetylcholine receptor antibody–negative patients will test positive for muscle-specific kinase antibodies.19,20

Treatment and current trends

As our understanding of autoimmune diseases progresses, new therapies are being suggested for juvenile myasthenia gravis. The classic first-line therapy is the anticholinesterase drugs. The most commonly used is pyridostigmine, but if the side effects are intolerable other options are available. High-dose corticosteroid therapy has been shown to be beneficial, and several studies have looked at their effect on slowing the progression of muscle group involvement.21 Because of the many complications of high-dose steroid therapy, the risks and benefits must be weighed on a patient-to-patient basis. See Table 1 for highlights of each treatment described here.

Because of the proposed role of the thymus in juvenile myasthenia gravis, thymectomy is frequently considered as part of the patient’s management. Four of five patients listed in Table 2 elected to undergo the procedure. They underwent transsternal thymectomy, a common approach that appears to offer similar results to the more recently accepted transcervical thymectomy.24 A large German study retrospectively measuring the long-term outcomes of 79 juvenile myasthenia gravis patients showed follicular hyperplasia in 89% of the 65 patients undergoing thymectomy and normal findings in the remainder. Remission occurred in 60% of patients who underwent thymectomy while only in 29% of those who did not.25 Both Lindner et al and Rodriguez et al determined that for best results, thymectomy should be performed within 12 months of the onset of symptoms.15,25 Based on our experiences and others’ reports, we recommend thymectomy for the treatment of both thymomatous and non-thymomatous juvenile myasthenia gravis when pyridostigmine and corticosteroids fail or cannot be tolerated.26 Physicians and patients should be aware that time to remission in thymectomized patients is quite variable, taking months for some patients and years for others.27 A phase III clinical trial is now underway to compare the effects of thymectomy combined with prednisone therapy to the effects of prednisone alone in patients with non-thymomatous myasthenia gravis.28

Each of our patients, before undergoing thymectomy, was treated with plasmapheresis (also known as plasma exchange), a procedure shown to improve outcome of thymectomy when administered preoperatively.29 It is known for rapidly resolving the symptoms of myasthenia gravis and is very useful during myasthenic crises. The procedure seems particularly effective in relieving the symptoms of muscle-specific kinase antibody–positive patients.40 Intravenous immunoglobulin G is a fairly new agent used in the management of juvenile myasthenia gravis, with indications and effects similar to those of plasmapheresis, including similar preoperative effectiveness.31 In most patients, plasma exchange and intravenous immunoglobulin G seem to be of little long-term benefit, though there
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage</th>
<th>Indications</th>
<th>Monitored Parameters</th>
<th>Advantages</th>
<th>Side Effects/Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyridostigmine bromide</td>
<td>1 mg/kg every 4 to 6 hours</td>
<td>First-line therapy for all MG patients</td>
<td>Blood pressure, electrolyte panel, blood glucose, mental status</td>
<td>Rapid improvement (15 to 30 minutes)</td>
<td>Muscarinic side effects including cramping, diarrhea, salivation, lacrimation, and bradycardia</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Begin 20 mg qod, increase by 10 mg every third to fifth day</td>
<td>Urgent or severe cases; unresponsive to pyridostigmine</td>
<td>Blood pressure, electrolyte panel, blood glucose, mental status</td>
<td>Remission or improvement in 65% to 75% of patients</td>
<td>Dyspepsia, gastric ulcer, hypertension, glucose intolerance, cataracts, fluid retention, weight gain, and so on</td>
</tr>
<tr>
<td>Thymectomy</td>
<td>Generalized MG; age puberty to 60 years; necessary if thymoma</td>
<td>CBC, hepatic function</td>
<td>Tolerated long term</td>
<td>4-6 week hospital stay; surgical complications</td>
<td></td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Initial: 50 mg daily; therapeutic: 2 to 3 mg/kg/day</td>
<td>If corticosteroids are contraindicated, ineffective, or poorly tolerated</td>
<td>CBC, renal function, blood pressure, electrolyte panel, hepatic function, cardiac and pulmonary function</td>
<td>No effect on liver function tests, CBC, electrolyte panel; Faster onset than azathioprine</td>
<td>Diarrhea, GI hemorrhage and perforation, increased infection rate, neutropenia; 2 to 6 months to clinical effect</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>500 mg bid, increased to 1 g bid after 4 weeks</td>
<td>Elevated antibody titers</td>
<td>CBC, electrolyte panel, blood pressure, renal function, hepatic function, cyclosporine blood levels, mental status</td>
<td>Faster onset than azathioprine; may be tolerated in patients refractory to other treatment</td>
<td>Renal dysfunction, hypertension, headaches, hirsutism, encephalopathy, seizures</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>3 to 5 mg/kg/d administered in 2 daily doses</td>
<td>Elevated antibody titers</td>
<td>Electrolyte panel, including Ca++ and Mg++</td>
<td>Rapid improvement</td>
<td>Impaired venous access after multiple exchanges; hematoma at the site of line placement, pulmonary embolism from venous thrombosis, electrolyte imbalance, pneumothorax, and hypotension</td>
</tr>
<tr>
<td>Plasmapheresis</td>
<td>5 to 6 Exchanges every other day</td>
<td>Prethymectomy, myasthenic crisis, rapid weakness, or progression of symptoms</td>
<td>Rapid improvement</td>
<td>Slow improvement than plasmapheresis, headache, transient flu-like symptoms</td>
<td></td>
</tr>
<tr>
<td>Intravenous immunoglobulin G</td>
<td>400 mg/kg/d for 5 days or 1 g/kg/d for 2 days</td>
<td>When plasmapheresis cannot be done or additional immuno-therapy is needed</td>
<td>CBC, serum intravenous immunoglobulin G, renal function, respiratory status, vital signs, signs of intravascular hemolysis</td>
<td>Rapid improvement; usually well tolerated and without complications</td>
<td>Slower improvement than plasmapheresis, headache, transient flu-like symptoms</td>
</tr>
</tbody>
</table>

Abbreviations: BID, twice daily; CBC, complete blood count; GI, gastrointestinal; MG, myasthenia gravis; QOD, every other day.
may still exist a select group of patients that seems to do well on chronic intravenous immunoglobulin G therapy. Currently ongoing is a phase III clinical trial investigating the effectiveness of intravenous immunoglobulin G in mild-to-moderate cases of myasthenia gravis patients, including children.28

Recently, there has been an increase in the use of non-steroidal immunosuppressants. Those most commonly used for juvenile myasthenia gravis are cyclosporine, azathioprine, and mycophenolate mofetil. Tacrolimus, another potent immunosuppressant, has also been recommended for the long-term treatment of myasthenia gravis in adults; hopefully, investigations currently underway will elucidate its role in younger patients. These drugs are often combined with a cholinesterase inhibitor and thymectomy. Like corticosteroids, these medications also have significant side effects, and patient response must be followed closely.34

Although there has been a paucity of controlled studies for the treatment of juvenile myasthenia gravis up to this point, new, aggressive treatments may be on the horizon. For example, current studies may show tacrolimus to be very beneficial in the pediatric populations, and hematopoietic stem cell transplantation may offer relief to patients unresponsive to surgery or medications.28

### Conclusion

Despite a lack of scientifically proven treatments for juvenile myasthenia gravis, it is important that physicians be able to recognize its myriad presentations, which vary widely in symptoms and severity, and be able to respond with appropriate diagnostic tests and treatments tailored to individual patient needs. As seen with our patients, prognosis is good in general, and spontaneous remissions seem to occur more often than in adult onset myasthenia gravis, and most patients who do not undergo total remission will lead relatively normal lives on some form of lifelong treatment. We are optimistic that ongoing and future research involving pediatric populations will further improve the prognosis of these patients.

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### References


