Juvenile Generalized Myasthenia Gravis: Presented as Unilateral Blepharoptosis and Successfully Managed with Pulse Intravenous Methylprednisolone

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ABSTRACT

Myasthenia Gravis is a rare autoimmune disorder of childhood and this is rarer in South Asia. We present a pre-pubertal 7 year old female child of seropositive Generalized Juvenile Myasthenia Gravis. She presented with unilateral blepharoptosis and later generalized symptoms appeared. Ice-pack test, Neostigmine challenge test and acetylcholine receptor antibody test were positive. Serum muscle specific tyrosine kinase antibody test was normal. She did not have thymic abnormalities. She did not respond to high dose (26 mg/kg/day) of Pyridostigmine and oral Prednisolone (2 mg/kg/day), but was successfully treated with a combination of pulse intravenous Methylprednisolone (30 mg/kg once a month for 6 months) and daily doses of oral Prednisolone (2 mg/kg/day) along with Pyridostigmine without significant side effects. This combination can be considered a potential inexpensive treatment for Juvenile Myasthenia Gravis in a resource limited area where other immunosuppressive treatments such as intravenous immunoglobulin is expensive and unaffordable.

KEY WORDS

Blepharoptosis, Child, Methylprednisolone, Muscle weakness, Myasthenia gravis

INTRODUCTION

Myasthenia Gravis (MG) is a rare autoimmune disorder of childhood. Juvenile Myasthenia Gravis (JMG) is MG presenting before 19 years of age.[1] In the majority of cases MG is caused by antibodies to the nicotinic acetylcholine receptor (AChR).[1] Patients with AChR antibodies are often referred to as seropositive. AChR antibodies are probably less frequent in pre-pubertal patients than in adolescent and adult patients.[2] The most frequent clinical presentation of JMG is with blepharoptosis, which is often associated with other ocular symptoms namely unilateral or asymmetric ophthalmoplegia, strabismus, and lid twitch, which may only be elicited after sustained upgaze.[3] Most children also develop generalized muscle weakness, which presents as painless fatigability of the bulbar and limb musculature, with resultant dysphonia, dysphagia, and proximal limb weakness. Weakness is often fluctuating and usually becomes more pronounced through the day and improves with rest. Occasionally, impairment of the respiratory muscles necessitates ventilatory support.[1] Although JMG shares many features with the more common adult MG, there are many differences.[1] JMG is primarily a clinical diagnosis with classical patterns of fluctuating weakness and fatigability.[1] A number of diagnostic tools are available to aid with diagnosis. These are ice-pack test, sleep test, anti-acetylcholine receptor antibodies, Tensilon test, repetitive nerve stimulation and single fiber electromyography.[4] Depending on clinical manifestation (ocular or generalized) and antibody

status (AChR-Ab-positive or negative), a combination of acetylcholinesterase (AChE) inhibitors such as Pyridostigmine, immunosuppression/immunomodulation with drugs such as steroids, IV immune globulin (IVIG), Rituximab and surgical therapy such as thymectomy are used for treatment of MG.[5] Because of existing therapeutic options, an early diagnosis is important.[5]

Paediatric presentation of MG is more common in Oriental than in Caucasian populations.[6] JMG cases are rarely reported from Nepal. Diagnosis and treatment of JMG in resource limited setting are quite challenging. Hence we present a case of generalized pre-pubertal JMG in a 7 year old female child reported from an area where this condition is not common. Ice-pack test along with Neostigmine challenge test were positive and these tests can be considered potential inexpensive tests for diagnosis where resources are scarce. She was treated with a combination of monthly pulse Methylprednisolone and daily oral prednisolone along with Pyridostigmine. This combination can be considered a potential inexpensive treatment for JMG in a resource limited area where other treatment options like IVIG or Rituximab are relatively expensive.

CASE REPORT

B.P. Koirala Institute of Health Sciences (BPKIHS) is a tertiary care medical university of Nepal which is the major referral center that provides health care to patients living in eastern part of Nepal and bordering districts of India. A 7 year old female child from Bihar India presented with complains of drooping of her eyelids noted since 2 months prior to presentation; initially involving her left eyelid followed by progressive involvement of her right eyelid, which worsened over a period of 2 months. Diurnal variation was also noticed. She would wake up and open her eyes fully then it used to start drooping within 30 minutes and by the passage of day she could barely keep her eyes open. There was also gradual change in the quality of her voice as she developed low volume and low pitched voice which made it difficult to understand her speech for last one month. Ten days prior to presentation, she also developed difficulty in swallowing solid food initially then later intake of liquids was a challenge for her because of aspiration. There was no complains of weakness of limbs or respiratory distress as such. There was no history of fever, abnormal body movement, bowel involvement, chronic drug intake, exposure to chemicals or any preexisting disease. Family history was unremarkable.

On examination her vitals were stable. On nervous system examination there was bilateral blepharoptosis (eye aperture 3-4 mm). The blepharoptosis got worse on sustained upward gaze (fig. 1). The movements of extraocular muscles were restricted in all directions, there was weakness of her muscles of mastication and she had difficulty in swallowing. Although there was no

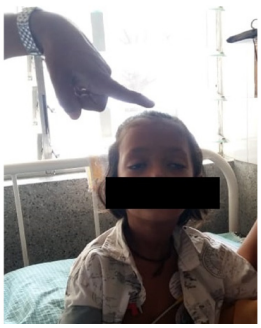

Figure 1. Severe Ptosis at presentation. This was the maximum child could open the eyes on upward gaze.

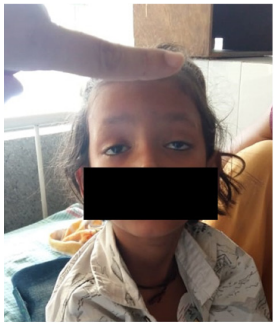

Figure 2. Slight improvement of Ptosis after Ice-pack test.

subjective complains of weakness of limbs, there was fatigable weakness of bilateral upper and lower limbs on examination. She showed progressive weakness of limbs on repeated exercise. There was low volume voice and oro-pharyngeal dysphagia.

Diagnosis of JMG was made that was initially based on ice pack test which is a simple bed side test. Child was made to sustain a maximum upward gaze for 30-60 seconds. Then she was asked to close her eyes and icepack was placed over her closed eyes for 2 minutes. On removal of icepack transient improvement of her blepharoptosis was noticed (fig. 2). Neostigmine challenge test was carried out due to unavailability of Tensilon. Intramuscular injection of neostigmine 0.2 mg/kg was administered. Prior to Neostigmine, injection atropine 0.025 mg/kg was given to prevent any cholinergic adverse effects. After 10 minutes of administering Neostigmine injection, dramatic improvement of her blepharoptosis was seen, hence the test was positive (fig. 3).

Figure 3. Improvement of ptosis noted after Neostigmine test.

Serum creatine kinase, thyroid function test and antinuclear antibody tests all were negative. Serum acetylcholine receptor (Ach-R) antibodies and muscle specific tyrosine kinase (MuSK) antibody values were 10.78 nmol/L (high) and < 0.18 U/ml (normal) respectively. Computed tomography (CT) neck and chest with contrast followed by MRI of head and neck with contrast were done to rule out thymoma and intracranial pathology. Both of them were normal and there were no signs of thymoma. The diagnosis of pre-pubertal juvenile generalized MG was made which was not associated with any thymus abnormalities.

The child was started on Pyridostigmine, 30 mg 8 hourly (8.5 mg/kg/day; 120 mg/day) along with Prednisolone at 1 mg/kg/day. As there was partial improvement, the dose of Pyridostigmine was increased to 30 mg 4 times in daytime (7 am, 11 am, 3 pm and 7 pm) after 2 days. Her feeding and speech improved a lot, but some degree of blepharoptosis and fatiguable limb weakness were persistent. Weakness of pharyngeal muscles was also fluctuating between the doses of Pyridostigmine. Since symptoms did not fully resolve, we increased the dose of Pyridostigmine every 2 days up to 90 mg 4 times a day (26 mg/kg/day; 360 mg/day) and increased the dose of Prednisolone to 2 mg/kg/day. Since child showed only partial improvement with Pyridostigmine and oral Prednisolone over 2 weeks, we started monthly pulses of Methylprednisolone at the dose of 30 mg/kg/day for 5 consecutive days every month. We continued oral Prednisolone at 2 mg/kg/day and Pyridostigmine 90 mg 4 times daily. We gave total of 6 cycles of monthly Pulse Methylprednisolone. Child showed improvement of all symptoms and she was symptom free including absence of blepharoptosis after 4 th cycle of Methylprednisolone. She gained 8 Kg weight in 4 months. Otherwise there were no other significant clinical or biochemical side effects of steroid. After 4 months, dose of oral Prednisolone was reduced to 1 mg/kg/day, and Pyridostigmine was brought down to 60 mg 4 times a day (6 am, 10 am, 2 pm and 6 pm) (240 mg per day; 11 mg/kg/day). On completion of 6th dose of Methylprednisolone, she was completely normal, she was still consuming 60 mg Pyridostigmine at 6 `am, 10 am, 2 pm and 6 pm, with no symptoms in between the doses. She did not have any blepharoptosis (fig. 4). She was then put on slowly tapering dose of oral Prednisolone.

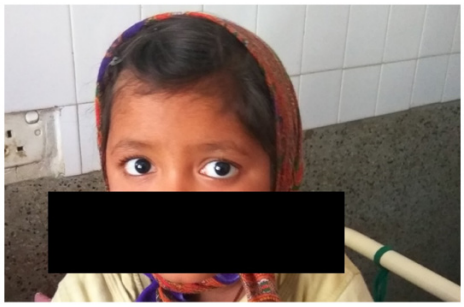

Figure 4. Total improvement of ptosis on 6 month follow up

DISCUSSION

MG patients are subdivided according to the occurrence of the first symptoms as pre-pubertal (first symptoms before the age of 12 years) and post pubertal (first symptoms after the age of 12 years).[7] Our case was 7 year old and was diagnosed to have pre-pubertal JMG. In a large study among JMG children in China that included 327 JMG cases, most frequent age group was 6-12 years, accounting for 56.6% of total cases.[8] Our child was also in the same age group. Although weakness may affect any muscle, MG has a distinct predilection for involvement of the extraocular muscles. MG patients are therefore categorized into two groups, the ocular MG (OMG) and the generalized group.[9] OMG is, by definition, MG restricted to the oculomotor muscles for 2 years without becoming generalized.[10] Ocular symptoms are common at onset both in ocular and generalized JMG. The most frequent clinical presentation of JMG is with blepharoptosis, which is often associated with other ocular symptoms namely unilateral or asymmetric ophthalmoplegia, strabismus, and lid twitch, which may only be elicited after sustained up gaze.[3] In a large study among JMG children in China, ocular symptom was the presenting symptom in 93.6% JMG cases, and ptosis was presenting feature in 72.8% cases.[8] In a Canadian case series on pediatric MG that included 57 children with MG, ptosis was the presenting feature in 82% of generalized JMG and 100% of ocular JMG cases. Unilateral ptosis was present in 21% cases of generalized JMG and 44% cases of ocular JMG.[11] Our child also had only ocular symptom in the form of unilateral ptosis at the onset of disease.

OMG in children is less likely to progress to generalized MG as compared to adults.[9] However; many children progress to generalized muscle weakness, which presents as painless fatigability of the bulbar and limb musculature, with resultant dysphonia, dysphagia, and proximal limb weakness.[1] In a series of three cases report of pre-pubertal JMG by Gadient et al., two cases presented with ptosis, one of them presented with unilateral ptosis and one presented with generalized weakness in addition to ptosis.[12] In another series of case report by O'Connell et al. a two year old child presented with unilateral ptosis that later progressed to bilateral and subsequently to generalized weakness; as happened in our child. Rest of the two cases in the same case series, a 13 year old girl and an eight year old by presented with ptosis, bulbar weakness and generalized muscle weakness from the begining.[13] Similarly, our child had only ocular symptoms at onset, unilateral ptosis being the first manifestation that later progressed to bilateral ptosis and then further progressed to bulbar and generalized weakness. She progressed in short time (2 months) to Generalized JMG.

A typical clinical symptom of abnormal neuromuscular transmission is fatigability.[3] Weakness is often fluctuating and usually becomes more pronounced through the day and improves with rest. Children are at risk of choking or aspiration and are at increased risk of chest infection.[1] Our child also had multiple symptoms with typical fatigable weakness. She developed bulbar symptoms like dysphagia, dysphonia, however, did not have choking, aspiration and chest infection. In a Canadian case series of JMG, bulbar symptoms such as dysphagia was very common feature that was present in all cases of ocular JMG and 65% cases of generalized JMG.[11] Our child had some degree of limb weakness as well. Her weakness was typically fluctuating, becoming worse as the day progressed and fatigable, becoming worse with the exercise.

To diagnose JMG, the combinations of a thorough history, repeated physical examinations, ice pack test, pharmacological tests and neurophysiological investigations (repetitive nerve stimulation tests), as well as antibody samples are helpful clues.[7]

In our case, history and clinical examination were typical of generalized JMG. Bedside and laboratory testing is often required to confirm or support (or refute) the clinical impression. There are always diagnostic challenges in resource limited settings due to scarcity of advanced, expensive and technically challenging tests. We did simple bedside test called ice-pack test. In the right sympotomatology, the ice-pack test can be an effective method of bedside diagnosis of MG and possibly prevent the use of expensive diagnostic medications with many unwanted and possibly dangerous side-effects.[14] The Ice-pack test was positive in our case. The Ice–pack test was used and was found to be reliably positive in case reports of ocular as well as generalized MG, both in children and adults, in case reports from different part of the world.[14,15] Ice-pack test has very high sensitivity and specificity for both ocular and generalized MG.[4] Ice-pack test has sensitivities of 94% and 82% and specificities of 97% and 96% for ocular and generalized MG respectively.[16]

The Tensilon test involves intravenous infusion of Tensilon, a fast-acting, short duration Cholinesterase inhibitor. This prevents the breakdown of acetylcholine, thereby increasing the concentration of the neurotransmitter at the neuromuscular junction. The patient is observed, and ideally a video recorded, looking for a transient improvement in previously documented weakness, for example, blepharoptosis and dysphonia.[1] Tensilon test has been reported to have sensitivities of 0.92 and 0.88 for ocular and generalized MG, respectively, as well as specificities of 0.97 for both forms of the disease.[17] In a case report by Gadient et al. Tensilon test was partially positive in an eight year old child with JMG.[12] In a Canadian study, Tensilon test was positive in 88% of generalized JMG cases and 100% of ocular JMG cases.[11] Since Tensilon was not available at our place, we used intramuscular Neostigmine for testing. Neostigmine test shows higher positivity than anti-AChR antibodies and repetitive nerve stimulation test in both ocular and generalized MG cases. Neostigmine test has been used and found to be reliable for diagnosis of MG in places where Tensilon is not easily available.[15,18] In an Indian study, the positivity rate of Neostigmine test was 93.4% for ocular MG and 97.9 % for generalized MG.[18] Our case responded well with complete resolution of ptosis with Neostigmine. Neurophysiological testing requires the skills of a trained paediatric neurophysiologist and is difficult in children due to reduced cooperation with needle placement. Repetitive nerve stimulation is more likely to be tolerated than single fiber EMG.[3] We were unable to do neurophysiological tests due to technical difficulties.

Peripubertal and post-pubertal children have in up to 90% positive Acetylcholine receptor (Ach-R) antibodies in case of generalized disease.[1] Antibodies that bind to the AChR are detected by co-precipitation of the patient's serum IgG with human skeletal muscle AChR. A positive assay for these binding antibodies in the appropriate clinical context is diagnostic of autoimmune MG, and these patients are seropositive.[19] Our child was seropositive for AchR antibody test and titer was high. In a study among Canadian children, AChR antibody was detectable in 67% children with generalized JMG and 44% children with ocular JMG.[11] In a Chinese study, 73.3% of the ocular JMG patients and 84.0% of generalized JMG patients were seropositive for AChR antibody.[8] The high frequency of seronegative MG in young children creates special problem. These are the very patients in whom discrimination between seronegative JMG and congenital MG is most important, yet limited history, frequent daytime sleeps, and imprecise clinical examination make a positive clinical diagnosis difficult.[19] MuSK antibodies are found in around 30-40% of AChR negative MG patients and are associated with specific clinical phenotypes. These patients usually respond well to immunosuppressive therapy but not as well to cholinesterase inhibitors.[20] MuSK antibodies seem to be less prevalent in JMG cases as compared to adults MG cases.[11,21] In a canadian study none of the JMG cases were positive for MuSK antibodies.[11] In a case report by Kalyan et al, an Indian JMG case was seronegative for MuSK antibodies.[22] However, MuSK antibody positive JMG has been reported.[23,24] Our patient tested negative for MuSK antibodies.

Contrast enhanced CT and later MRI was done that ruled out presence of thymic pathology in our child. In JMG, thymic pathologies such as thymic hyperplasia or thymoma can be present.[8,24,25] Indication for thymectomy include the presence of a thymoma. All patients with MG with thymoma should undergo surgery to remove the tumor.[25] The value of thymectomy in the treatment of pre-pubertal patients with MG is unclear, but thymectomy should be considered in children with generalized AChR antibody positive MG if the response to Pyridostigmine and immunosuppressive therapy is unsatisfactory; or in order to avoid potential complications of immunosuppressive therapy.[25]

Pyridostigmine is the first-line therapy in JMG for long time use and is administered orally.[26] Prednisolone, Azathioprine, Mycophenolate Mofetil, IVIG, Rituximab, Tacrolimus, Cyclosporine and plasma exchange are the usual immunosuppressive treatment recommended for the treatment of MG.[7,19,27] Many patients require combination of treatments such as Pyridostigmine, steroid, IVIG and steroid sparing agents, with variable response.[11] Thymectomy appears to provide a high rate of remission and improvement in children with AchR positive JMG, when children do not tolerate or respond well to medical treatment or when MG is associated with thymic

abnormalities.[7,28] Further prospective multicenter studies are necessary to clarify the efficacy and side effect profile of immunosuppressive therapies and to determine whether thymectomy is indicated for all children with generalized JMG. More information about the immunologic, genetic, and molecular differences between patients may determine the best treatment for individual patients.[24] Pyridostigmine dose should be adjusted as needed based on symptoms.[25,26] Our child was initially treated with Pyridostigmine. Acetylcholine esterase (AChE) inhibitors lead to a prolonged activity of acetylcholine (ACh) in the synaptic cleft by blocking hydrolysis of ACh. Initial dosage of Pyridostigmine is 0.5 to 1 mg/kg/d every 4 to 6 hours, a daily increase up to 5 to 7 mg/kg/d is possible up to the maximal of 300 mg/d.[26] In some cases, higher doses may be used.[26] Our case received 26 mg/kg/d (360 mg/d) of Pyridostigmine. Surprisingly, there was no any adverse event and child tolerated the dosage well. Unfortunately, her symptoms did not respond fully even with the high dose Pyridostigmine. Then we decided to treat her with immunosuppressive therapy.

We started immunosuppressive treatment with oral Prednisolone, however, child responded only partially. Other standard immunosuppressive treatments like IVIG, Rituximab, and plasma exchange are not easily available, and when available, most people cannot afford them at resource limited areas. In our center, although these options were available, parents could not afford these treatment options.

High-dose intravenous Methylprednisolone is used in many autoimmune disorders to provide therapeutic benefit without the side effects of chronic immunosuppressive therapies. Sustained improvement lasting months following various regimes of pulse Methylprednisolone have been reported.[29-32] Some patients show little response.[32] Due to easy availability and inexpensive cost, parents of the current child preferred to use intravenous (IV) Methylprednisolone. Therefore, we (treating team and parents) decided to give monthly pulse of IV Methylprednisolone for 6 months with slowly tapering maintenance dose of oral prednisolone. That treatment caused significant improvement in signs and symptoms and child was totally symptom free on 6 month follow up. We were able to bring down the dose of oral Prednisolone and Pyridostigmine after immunosuppressive treatment with monthly pulses of Methylprednisolone.

In conclusion, this was a case of generalized pre-pubertal JMG in a 7 year old female child reported from an area where this condition is not common. Children can have varied presentation. Localized symptom such as belpharoptosis can progress to generalized MG as happened in this child. Ice-pack test and Neostigmine challenge test are potential inexpensive tests for diagnosis where resources are scarce. As seen in this child, children may not respond to pyridostigmine alone and may require immunosuppressive treatments in addition. A combination of intravenous monthly pulse Methylprednisolone and daily oral Prednisolone along with Pyridostigmine can be considered a potential inexpensive treatment for Juvenile MG in a resource limited area where other treatment options like IVIG and other immunosuppressive treatments are relatively expensive and unaffordable.

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