

**Case Report****Juvenile Ocular Myasthenia Gravis: A Case Report****Ferry Yulianto<sup>1,\*</sup>, I Gusti Ngurah Made Suwarba<sup>1,\*</sup>, Dewi Sutriani Mahalini<sup>1</sup>, Anak Agung Mas Putrawati Triningrat<sup>2</sup>, Made Paramita Wijayati<sup>2</sup>**<sup>1</sup>Sanglah Hospital-Department of Pediatrics, Udayana University, Denpasar-Bali, Indonesia<sup>2</sup>Sanglah Hospital-Department of Ophthalmology, Udayana University, Denpasar-Bali, Indonesia**Email address:**

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**Abstract:** Myasthenia gravis is a chronic autoimmune disease of neuromuscular blockade, characterized by rapid fatigability of striated muscle. Estimated incidence has been reported at 1/200,000 to 1/1,000,000 worldwide, but its incidence in Indonesia is not clearly recorded. We report a rare case of juvenile ocular myasthenia gravis which is considered rare in child population. The objective of this case report is to describe the proper assessment of its clinical presentation. Patient is an eleven years old boy who had ptosis and ophthalmoplegia on both sides for three weeks duration. Its complaint was exaggerated with sustained gaze on daily activities. Ptosis was triggered quickly after being induced by fixated upgaze without blinking and improved after ice pack was put on his eyelids for five minutes. However, his vision was preserved and no slurred speech, dysphagia or limb weakness on physical examination. Neostigmine test showed positive result and rapid nerve stimulation test also revealed with significant decrement on the affected eyelid muscles. No thymoma was seen on chest CT scan and thyroid function test was also normal. Hence the diagnosis was made and pyridostigmine was started for its medication. This report present a rare case of juvenile ocular myasthenia gravis. Early recognizing by some diagnostic modalities confirms its diagnosis so that treatment could be started to control the muscle weariness and improving patient's quality of life.**Keywords:** Juvenile Ocular Myasthenia Gravis, Ptosis, Child

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**1. Introduction**

Myasthenia gravis is a chronic autoimmune disease of neuromuscular blockade, characterized clinically by rapid fatigability of striated muscle, particularly extraocular and palpebral muscles and those of swallowing [1]. The release of acetylcholine (ACh) into the synaptic cleft by the axonal terminal is normal, but the postsynaptic muscle membrane (sarcolemma) or motor end plate is less responsive than normal. This is due to antibodies against the postsynaptic acetylcholine receptor (AChR), leading to an abnormal architecture/folding pattern of the postsynaptic membrane, as well as a decreased number of receptors to which acetylcholine can bind [2, 21]. A decreased number of available ACh receptors is as a result of circulating

receptor-binding antibodies in most cases of autoimmune myasthenia [1, 2].

The immune-mediated nature of Myasthenia Gravis was suspected as early as 1960, when Simpson speculated that it was an autoimmune disease with antibodies directed against skeletal muscle Acetylcholine Receptor (AChR) [3]. The exact prevalence and incidence of juvenile myasthenia gravis are not known. Estimated incidence has been reported at 1/200,000 to 1/1,000,000. The disorder is uncommon in Europe and North America. In the Asian population, a much higher proportion of cases with mainly ocular manifestations occurs in children below 15 years of age.

The incidence of juvenile myasthenia gravis in Indonesia is not clearly recorded. Data from RSCM (Cipto Mangunkusumo Hospital) in 2010 – 2011 recorded 94 all ages Myasthenia Gravis cases [4]. From 2010 – 2014, there were 55

patients diagnosed with Myasthenia Gravis in Eye Center Hospital in Bandung, West Java, Indonesia with 77% of patients aged over 50 years and 71% being female.

Ocular myasthenia gravis accounts for approximately 25% of all juvenile myasthenia gravis patients and is most frequent in children of Chinese and southeastern Asian descent, suggesting an ethnic genetic predisposition. In addition, prepubertal patients are more likely to have ocular only myasthenia, whereas a majority of postpubertal patients with myasthenia will have generalized symptoms [5]. In this case, our patient has just started the pubertal phase and has the typical mainly ocular manifestation which with no involvement of limb weakness.

This case report presents a myasthenia gravis and its clinical manifestation occurred in childhood which considered rare in pediatric population. It's early subtle manifestation is not conspicuously seen makes it challenging to be diagnosed in early phase since some of this kind of disease may progress.

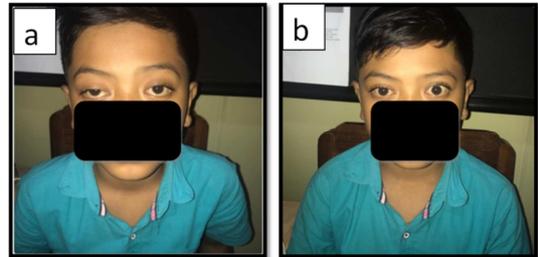
## 2. Case Report

We report a rare entity, we describe as a juvenile ocular myasthenia gravis. An 11 years old boy who was referred by an ophthalmologist from regional hospital in Bali for further evaluation and management of ptosis of both eyes, more on the right. The patient had no history of fatigability, difficulty sucking on pacifier, or inactivity during infancy. The birth history was unremarkable and no family history of weaknesses of limbs.

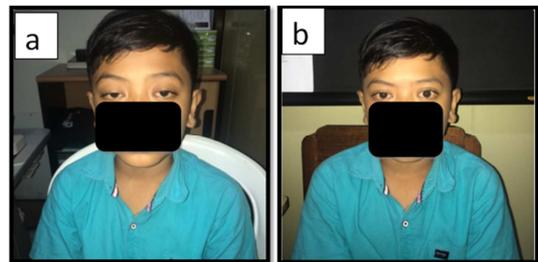
Patient had complaint of fatigue of both eyelids since 3 weeks prior to consultation. Patient's mother noticed right eyelid was more affected than the other side. This condition was varied by time and daily activities. Patient was okay after waking up in the morning, but eyelids weariness felt usually starting in the morning around 9 AM. Resting by closing both eyes for several minutes or putting the ice packs on it aborted its weariness. But the condition came back again especially when he staring his gadget or television for some time, the longer he staring, the more fatigue he felt. This circumstance interfered his daily activities, especially in the afternoon when he spent most of his time at the school. He could read and see clearly as before so the vision was preserved. However he had difficulty to take a glance to either right or left of her vision without moving his head. No weaknesses of both upper and lower extremities. No slurred speech or hoarseness. He had no difficulty in swallowing or breathing as well. There was no history of traumatic event on head or face beforehand.

During consultation at our hospital, patient was assessed by pediatric neurologist and neuro – ophthalmologist initially. On examination, visual acuity was 6/6 on both eyes. Distance between upper lid margin and light reflex or MRD (Marginal Reflex Distance) was +1 on right palpebra versus +2 - +3 on the left as shown at figure 1. We let the patient rest by let him closing his eyes for 10 minutes. The result was ptosis was improved on both palpebra (right palpebra was more affected). Afterward, patient was instructed to sustain upgaze on fixated without blinking. As shown at figure 2, the ptosis was

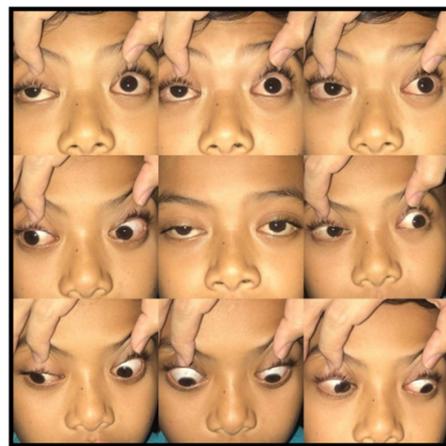
triggered quickly. We confirmed the ptosis by putting the ice pack on the eyelids area for 5 minutes. Again, the ptosis condition improved there after. We further examined for extra - ocular muscle test, which showed ophthalmoplegia on both sides, as shown at figure 3. Conjunctiva, cornea, anterior chamber, iris, pupil, lens, vitreous, intraocular pressure and fundusoscopic findings were unremarkable.



**Figure 1.** a). Ptosis seen on first visit at outpatient Department, and b). lessen after taking 10 minutes rest. (All pictures were taken with parent's consent and child permission).



**Figure 2.** a). Both eyelids lowering down after took 5 minutes fatigue test, and b). ptosis fading away after ice pack was put on the upper eyelid for 5 minutes.

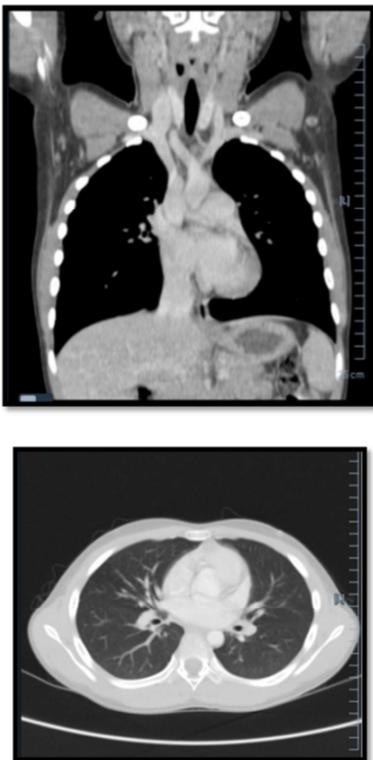


**Figure 3.** Ophthalmoplegia seen on extraocular muscles movement examination.

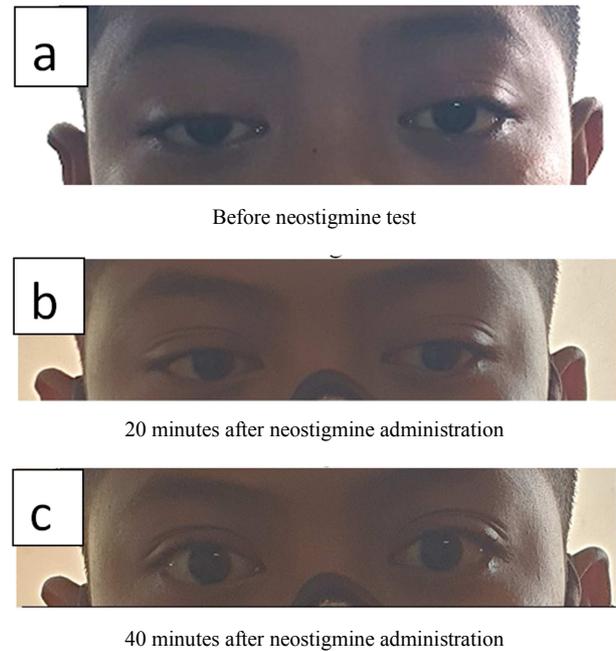
While counting out loud (1 to 50), no dysarthria or slurred speech occurred in this patient. Patient was asked to make a high – pitched (“eeee”) sound to assess weakness of the laryngeal muscle, but the hoarseness did not occur. Patient could breathing normally with no sign of respiratory distress. Hand grip and sustained elevation of leg while lying supine could be performed well even against some resistance from the examiner. Gait is not affected. Muscle strength and general sensations were maintained equally on both sides in this

patient.

Complete blood count and thyroid function tests were within normal limit. Multi Slice CT Scan (MSCT) of the chest was included to evaluate thymoma which could be one comorbid in myasthenia patient. As shown at figure 4, neither mediastinal mass nor thymoma seen in this patient. Neostigmine test as a pharmacological diagnostic modality of myasthenia gravis was performed for observation of ocular alignment. This pharmacological analysis was conducted bedside at the hospital due to risk of adverse drug effects. Single dose of 0.5 mg of methylsulfate neostigmine was administered intramuscularly. Ptosis was improved and resulted in marked improvement of both palpebral ptosis and improvement in both eyes movements after 40 minutes after injection as shown at figure 5. There was no adverse reactions such as bradycardia, dysrhythmia, hypotension or hypersensitivity reaction observed neostigmine administration. Finally, electromyography study with Repetitive Nerve Stimulation (RNS) was done in this patient. The study applied specifically on right orbicularis oculi muscle and right abductor digiti minimi muscle. The decrement test was negative on right abductor digiti minimi muscle (this muscle is innervated by ulnar nerve) while right orbicularis oculi muscle showed positive result with maximum decrement of 33.6% (aforementioned muscle is innervated by the zygomatic and temporal branches of facial nerve). Based on this study, neuromuscular junction lesion was concluded objectively. Based on the history taking, physical examination and diagnostic findings, the patient was diagnosed with Juvenile Ocular Myasthenia Gravis.



**Figure 4.** Chest Axial Multislice CT Scan showed no mediastinal mass, thymus is within normal size and its parenchymal density was normal.



**Figure 5.** Neostigmine intramuscular test. a). Ptosis is prominent before the test. b). Ptosis improved at 20 minutes after neostigmine administration and c). resolution of ptosis after 40 minutes.

One of the acetylcholinesterase inhibitors, pyridostigmine bromide, was prescribed at maximum dose of 60 mg per dose every 6 hours (6 mg/kg/day) altogether with vitamin B12 (methylcobalamin). During regular follow up, the condition was improved. The patient responded well with the treatment with ptosis and ophthalmoplegia reduced gradually. Patient need to have a regular follow up to control the medication and for observation since the disease could recur.

### 3. Discussion

This case report present a 11 years old boy patient with ptosis. Ptosis is a droopy eyelid that can be unilateral or bilateral. The amount of ptosis can be determined by measuring the distance between the upper and lower eyelids and the margin-reflex distance (MRD). MRD is the distance from the margin of the upper eyelid to the corneal light reflex when the eye is in primary position. Ptosis may occur in children as a result of several other disorders. Although ptosis in children is often an isolated finding, it may occur in association with other ocular or systemic disorder. It is also important to differentiate congenital ptosis from acquired cases.

Pseudoptosis could be inadvertently seen when the globe is microphthalmic or hypotropia (vertical strabismus with downward turning of the eyeball), but this patient clearly present with normal globe size and no strabismus seen during physical examination. Mechanical ptosis secondary to lid tumors is one of the etiology which was not owned in this patient.

Congenital ptosis is associated with an abnormal levator muscle muscle (the muscle responsible for lifting the eyelid), which normal striated muscle fibers are replaced by fibrosis,

resulting in an inelastic, weak muscle. Ptosis occurred just few weeks prior to consultation at our institution and lid creases are present. Hence, a group of disorders associated with congenital ptosis could be excluded in this patient.

Systemic acquired disorders which can be presented with ptosis include myogenic ptosis (myasthenia gravis and chronic progressive external ophthalmoplegia), neurogenic ptosis (Horner syndrome) and botulism. Limb muscle strength is well preserved and no slurred speech or difficulty in swallowing found in this patient, hence chronic progressive external ophthalmoplegia and botulism could be excluded. Pupillary reflexes are maintained and both iris color are same in color bilaterally. These findings are not pointing to Horner syndrome as well. Based on the physical examination and diagnostic modalities presented in this patient, diagnosis of juvenile ocular myasthenia gravis was made.

When myasthenia gravis present before 19 years of age, it is termed clinical Juvenile myasthenia gravis. Juvenile myasthenia gravis is a rare condition of children and has many clinical features that are distinct from adult myasthenia gravis. Myasthenia gravis in child population is different in various ethnic groups. Oriental-Chinese ancestral is more common than Caucasian group [6]. It's onset also different between age group. In Caucasians myasthenia gravis is more liable to present in adulthood with prepubertal onset is less than 10% cases [10, 11]. In contrast to Chinese populations, half of all myasthenia gravis cases occurred in childhood age peaked at 5-10 years old [7]. Occurrence is more often to female predominance in peri/post pubertal patients with main presentation share similarities with adult type myasthenia gravis [8, 9]. Contingency in prepubertal patients showed equal male/female ratio and manifestation is more likely as ocular myasthenia [14, 15].

There are two types of myasthenia gravis clinically. The ocular myasthenia gravis type, which predominantly occurs in prepubertal children follows the oculomotor muscles weakness without any other systemic manifestation [17]. Juvenile myasthenia gravis usually presented with ocular type. Ocular manifestation, especially ptosis is the most common chief complaint upon consultation. Altogether with other ophthalmic sign and symptoms such as ophthalmoplegia and strabismus, can be provoked with sustained upgaze for few minutes [12]. These symptoms, if severe, they may cause persistent amblyopia [13]. Weakness is often fluctuating and usually becomes more projected through the day and improves with rest. Otherwise in generalized type, commonly occurs in adult populations. Progression from ocular to generalized type is less frequent in prepubertal children [20, 22]. Gradual development of generalized muscle weakness, which presents as musculature fatigue, with resultant of dysphonia, dysphagia, and proximal limb weakness should be an alert for physician for the generalized type entity. The lethal impairment of respiratory muscle weakness (known as 'myasthenic crisis') occasionally entails ventilatory support.

The diagnosis of ocular myasthenia gravis can be made with an ice-pack test, in which ice is placed on the affected eye for 2 minutes if the patient has ptosis or for 5 minutes if the

patient has ophthalmoplegia. The test is positive if there is evidence of an improvement in symptoms, as shown in this patient [22].

Grave disease, a thyroid-related autoimmune disease could be presented with eyelid lag and weakness of extraocular muscle. Hence thyroid function hormone should be evaluated as this abnormality could become one of its differential diagnosis, but thyroid hormone in this patient is still within normal limit.

Pharmacological test such as pyridostigmine, edrophonium (Tensilon®), or neostigmine test can also be performed. These drugs are anticholinesterase, competing with cholinesterase in the neuromuscular junction, which generates an increase in the concentration of Ach and facilitates its binding with the receptors. The difference between these tests is the effect onset time and its duration. With fastest onset is seen with edrophonium [22]. Intramuscular administration of 1.0 – 1.5 mg methylsulfate neostigmine for adult is considered safe. Atropine (0.5 mg) could be applied intramuscularly if there are any muscarinic cholinergic receptor-mediated side effects. For children, neostigmine should be reduced to 0.02-0.03 mg/kg, while total amount should not more than 1.0 mg. Test should be performed at the muscle with significant symptoms and baseline of muscle tone should be firstly recorded, which is repeated every 10 minutes for 1 hour [23]. Ptosis degree was improved after administration of neostigmine in this patient.

Detection of antibodies to the AChR supports the diagnosis of juvenile myasthenia gravis [21]. AChR antibody are less frequent in prepubertal patient than in adolescent and adult patients [16, 19]. Positive results could be detected in about 50-60% patients with ptosis and other ocular sign, while 85-90% patients with generalized sign would have positive outcomes [23]. Some of these children who are negative for AChR antibodies will have "low affinity" antibodies to the AChR which were not detectable using the standard assays [24]. A variable percentage (0–49%) of myasthenia gravis patients without AChR antibodies are found to have antibodies against another neuromuscular junction protein, the muscle-specific kinase MuSK [25, 27]. MuSK positive myasthenia gravis is rare in children, and these children represent a distinct subgroup of juvenile myasthenia gravis, with a marked female predominance. MuSK antibodies appear to be associated with more severe disease with prominent facial and bulbar weakness and frequent respiratory crises [26]. Patients without antibodies to AChR or MuSK are described as having seronegative myasthenia gravis. This serology determination is not available in our country hence the diagnosis was made with other modalities.

Repetitive Nerve Stimulation (RNS) is an electrical stimulation to nerves, such as facial, accessory, axillary and ulnar nerves, for myasthenia gravis diagnosis, with repetitive and high-powered low frequency (2-5 Hz) signal. Compound muscle action potential (CMAP) over the testing muscle will be recorded. The duration of stimulation is about 3 seconds. The decrement of CMAP of myasthenia gravis is measured by comparing the CMAP value of the fourth or fifth stimuli to that

of the first stimulus. Diagnosis will be concluded as positive when there is more than 10% reduction. Myasthenia gravis patients on acetylcholinesterase inhibitor medication should not receive this test until 12-18 hours of washing out [22]. There was decrement of 33% noted after RNS examination in this patient which categorized in positive result.

Although thymoma in children is rare, the thymus must be imaged (usually by CT) once juvenile myasthenia gravis has been diagnosed. In adult, there are approximately 20-25% myasthenia gravis patients suffer also from thymic tumors while 80% have abnormal condition of thymus. Amongst the myasthenia gravis patients with thymic tumors, 20-25% of them present myasthenia gravis symptoms [28]. AChR seropositive myasthenia gravis is frequently associated with changes in the thymus, with histological changes and in vitro effects suggesting that the thymus plays a pathogenic role [28, 33]. Thymus hyperplasia is the commonest abnormality of the thymus in JMG [29]. Thymoma is particularly rare in prepubertal children [30]. MSCT was done in this patient and thymoma was not found in this patient.

Treatment of juvenile myasthenia gravis has largely been extrapolated from adult studies and experience with adult patients. There are few studies looking specifically at interventions in children, particularly prepubertal children. Given the evidence that prepubertal juvenile myasthenia gravis may behave quite differently in terms of disease severity and progression, this may impact on necessity for treatment and treatment response. Acetylcholinesterase inhibitors are first-line treatment in juvenile myasthenia gravis and provide symptomatic relief. In mild cases and in some cases of ocular myasthenia gravis, acetylcholinesterase therapy may be sufficient. The first line treatment is pyridostigmine in children or neostigmine in neonates [14]. Pyridostigmine is a long-acting cholinesterase inhibitor that is commonly used. Initial dosage is 0.5-1mg/kg/day is given usually 4-6 times per day and is tailored to effects. A daily increment up to 5-7 mg/kg/day is possible with maximum dose of 300 mg/day. Side effects include nausea, diarrhea, stomach cramp, bradycardia and increase of oral and respiratory secretions [14, 23]. This patient was given in dose of 6 mg/kg/day (60 mg every 6 hours) to maintain its therapeutic effect. Other strategy is using immunosuppressive therapies. Corticosteroid, steroid sparing agents like azathioprine, cyclosporine A, cyclophosphamide even plasma exchange / IVIG administration had been tried in some studies and showed promising results. Prednisone and prednisolone are the first-line therapy in children with persisting symptoms with the starting dosage is 0.5-1mg/kg (maximum 30 mg/day), with a possible increase up to 2 mg/kg/day (maximum 60-80mg/day) [31].

Outcomes in juvenile myasthenia gravis have improved significantly over the last decade, with better recognition, diagnosis, and more effective therapies, and long-term prognosis is good [32]. Children with juvenile myasthenia gravis exhibit higher rates of remission than adults. This includes spontaneous remission and remission following a period of drug therapy. Prepubertal children have the highest

rates of spontaneous remission. Ten-twenty percent of myasthenia gravis patients in ocular form will spontaneously heal, while 20-30% only experience extraocular myasthenia gravis. For the rest, more than 85% will gradually spread the signs of medulla oblongata and skeletal muscle, developing form in 3 years [23]. Remission rates also appear to be influenced by ethnic origin [18]. As shown in this report, the patient responded well with given pyridostigmine with satisfying result.

## 4. Conclusion

Juvenile myasthenia gravis is a rare, autoimmune condition of childhood that shares many characteristics of clinical presentation and management strategies with the adult form of the disease. However, as described in this case report, there are many important aspects that are specific to the paediatric population, in particular the distinct clinical features of the prepubertal presentations and response to therapy. Further studies looking at efficacy of therapies in pre- and postpubertal children are needed to better understand and support this distinct group of patients.

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