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A TYPICAL CASE OF CHILDHOOD OCULAR MYASTHENIA GRAVIS: A LITERATURE REVIEW FROM OPHTHALMOLOGY PERSPECTIVE

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ABSTRACT

Background: Childhood ocular myasthenia gravis (MG) is a rare autoimmune disease that has a benign course and provide a good overall prognosis. Diagnosis of ocular MG especially in children is often difficult especially in younger age group as the symptoms may be subtle and may mimic other pathology. There are many articles discussing MG in general, but only a handful elaborating on childhood ocular MG. This article is discussing a typical case of childhood MG and a review of current clinical approach particularly from ophthalmology point of view.

Case Report: A one-year-old Malay girl who was previously well, presented with 2 weeks history of left eye ptosis and intermittent exotropia following a brief episode of fever. A provisional diagnosis of ocular MG was made. Unfortunately, the patient defaulted pediatric neurology follow up for confirmatory investigations. She came back 2 years later with bilateral ptosis. Upon her second presentation, blood investigation for acetylcholine receptor antibody showed positive result and finally she was diagnosed to have ocular MG. She was co-managed with a pediatric neurologist and was treated with oral pyridostigmine. Satisfactory improvement of ptosis was achieved with no amblyopia. There was no features of systemic MG during 2 years follow up.

Conclusion: Although this is a typical presentation of childhood ocular MG, there are many interesting and useful learning points particularly from an ophthalmology point of view.

Keywords: Ocular myasthenia gravis, childhood, ptosis, autoimmune disorder, neuromuscular disease

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1.0 Introduction

Myasthenia gravis (MG) is a rare autoimmune disorder that affect skeletal muscle by blocking or damaging the acetylcholine receptor at the neuromuscular junction. As of many other autoimmune diseases, the cause of this condition is not well understood. MG can affect children as young as one year old and adult until fifth to sixth decade of life (Huang et al., 2013). Childhood or juvenile MG is a subtype of this condition that is defined as autoimmune MG occurs in children less than 19 years old (Finnis & Jayawant, 2011). The most common presentation in childhood MG is similar to adult which is ocular manifestation such as ptosis and strabismus (VanderPluym et al., 2013). However, it is not uncommon for the children to present with generalised symptoms such as bulbar and proximal muscular weakness (VanderPluym et al., 2013). This article is focusing on a discussion of a child with ocular MG with typical presentation and a review of latest clinical practice.

2.0 Case Report

A one-year-old Malay girl presented with 2 weeks history of progressive worsening of ptosis over the right eye. The right eye ptosis was associated with intermittent outward deviation of the eyeball. It was preceded by a self-limiting high-grade fever, which lasted for 2 days. However, the cause for the fever was unknown since the parents did not seek any treatment. There was no skin lesion accompanied the fever.

The child was diagnosed with a provisional diagnosis of ocular MG. She was referred to a visiting pediatric neurologist for a confirmatory investigations. Unfortunately, the child did not turn up for the pediatric neurology appointment and defaulted her appointment at ophthalmology clinic after 3 months of her presentation.

After 2 years, her parents brought her back to ophthalmology clinic with a complaint of bilateral ptosis for one month. Retrospectively, according to her parents, the right eye ptosis, which developed during her first presentation, has a complete spontaneous resolution after 3 months. For this current presentation, the ptosis was associated with intermittent strabismus with no preceding fever or illness. These symptoms were less noticeable in the morning but became more prominent towards the evening.

Apart from the ptosis and strabismus, the child has no symptoms or signs of generalised involvement of MG. She has no history of choking or difficulty in swallowing and no proximal myopathy. Within the past 2 years, she had no severe illness that warrant hospital admission. There were also no neurological symptoms reported such as nausea, vomiting, headache, impairment of balance or choking.

Perinatally, she was delivered full term through normal spontaneous vaginal delivery with birth weight of 2.45 kilogram. Maternal antenatal history was unremarkable. The child was healthy

and no history of hospital admission post-delivery. She was the only child in the family and no significant family history with similar problem.

On examination, the child appeared comfortable and not lethargic. Visual acuity was 6/24 when she first presented 2 years ago and during her current visit, her visual acuity was 6/7.5 bilaterally. The most apparent ocular finding was marked ptosis of both eyes with slight chin up head posture (Figure 1). Left eye ptosis was more severe compared to right eye but both eyelids did not cover the pupillary axis. The palpebral aperture measured 7 mm on the right and 6 mm on the left. The superior margin-reflex distance was 3 mm on the right and 2 mm on the left. Levator function measured 12 mm bilaterally. She was able to elevate both eyelids initially but unable to sustain after a certain period. Both upper lid crease were present but faint and eyelid elevation were aided by frontalis muscle. Pupils were equal in size, round and reactive to light with no relative afferent pupillary defect. She was able to close both eyes adequately with no lagophthalmos and no peek sign. Eye movement examination revealed no diplopia with no weakness of the extraocular muscles. Cover uncover test revealed an intermittent alternating exotropia with deviation approximately 5-10 prism diopter. Cyclorefraction showed +0.50/-0.50x180 in the right eye and plano/0.50x180 in the left eye. Anterior and posterior segments examination were normal in both eyes.

All features were confined to the ocular muscles and there was no proximal muscle weakness or generalised fatigue and no bulbar weakness. Neurological examination apart from ocular findings were unremarkable.

Based on suggestive history and examination, a diagnosis of ocular MG was suspected. A positive acetylcholine receptor (AchR) antibody assay (titre 2.10nmol/L) performed a few weeks later supported the diagnosis. Blood investigation for thyroid function test and thyroid antibody were taken to rule out autoimmune thyroid disease but the results were negative. She also underwent computed tomography thorax examination but the finding showed no enlargement of thymus.

She was co-managed with a visiting paediatric neurologist. The patient was treated with oral pyridostigmine. After 2 months of treatment, there was resolution of strabismus with satisfactory improvement of the ptosis. For this current presentation, she was compliant to follow up visit. At 2 years follow up, there was no worsening of ocular features with no features of systemic MG.

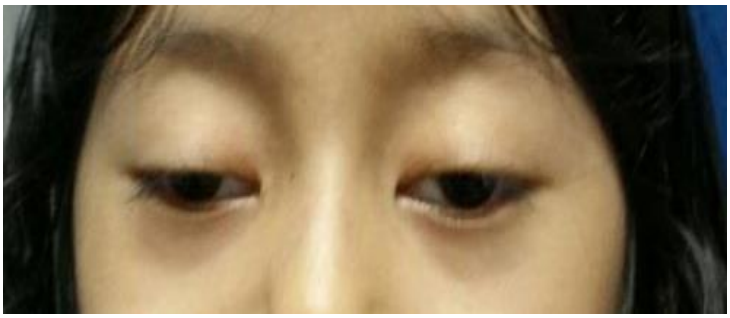

Figure 1: Patient profile showing bilateral ptosis at primary position.

3.0 Discussions

Ocular MG is a subtype of MG that is classified as Osserman I or more recently classified as Myasthenia Gravis Foundation of America (MGFA) I (Lin, Chen, Jou, & Woung, 2017). Ocular MG involvement is confined to the extraocular muscles, levator palpebral superioris muscle and sometimes orbicularis oculi muscle (Lin et al., 2017). Respectively these muscles involvement may cause strabismus, unilateral or bilateral ptosis and weakness of eyelid closure. The diagnosis of ocular MG is considered when generalised symptoms are not present after 2 years of onset (Luchanok & Kaminski, 2008). This is based on many epidemiological studies, which showed more than 80 percent of generalised MG developed within 2 years of diagnosis (Luchanok & Kaminski, 2008; Smith & Lee, 2017).

Apart from ocular and generalised MG that occur in both children and adult, a few subtypes of childhood MG was recognised, namely, neonatal MG, juvenile MG and congenital MG. Neonatal MG, is an immune mediated type that manifest transiently during the neonatal period. The etiology is similar to adult MG where there is an autoantibodies activity at the neuromuscular junction, however the antibodies exist as a result of maternal placental transfer (Finnis & Jayawant, 2011). Another type of MG is juvenile MG where there is a presence of antibodies against acetylcholine receptor. It affects children from 1 until 19 years of age (Finnis & Jayawant, 2011). Juvenile MG may be associated with other autoimmune diseases such as Hashimoto's thyroiditis and polymyositis (Kanazawa, Shimohata, Tanaka, & Nishizawa, 2007; Mohamed & SS, 2017). The last type is congenital MG, although its presentation is similar to adult and other types of childhood MG, the etiology is different (Engel, Shen, Selcen, & Sine, 2015). There is a structural abnormality at the neuromuscular junction that causes the abnormal acetylcholine transmission (Engel et al., 2015). This non immune mediated cause of MG affect children from birth (even younger than juvenile MG) and may have affected family members (Engel et al., 2015). In this article, childhood MG is referred as juvenile MG.

The overall incidence of MG worldwide is around 0.3 to 2.8 cases per 100 000 population (Deenen, Horlings, Verschuuren, Verbeek, & van Engelen, 2015). It was estimated that juvenile MG accounted for 10 to 15% of all MG patients in a Western study (Phillips, Torner, Anderson, & Cox, 1992). There is no recent data regarding epidemiology of MG in Malaysia. In a review done in 1980 at a local university hospital, the incidence of MG in Malaysia was found almost similar to the Western population (Tan & Loh, 1980). Juvenile MG was found in 11% of all MG patients with no gender difference (Tan & Loh, 1980). MG in general was more prevalent among Chinese ethnics compared to Malay and Indian (Tan & Loh, 1980). This is comparable with a demographic study in Singapore done in 2003 (Au, Das, & Tjia, 2003; Tan & Loh, 1980).

MG patient who presented at young age usually has distinctive characteristics compared to adult MG. The children are more likely to have ocular manifestation only (Au et al., 2003; Finnis & Jayawant, 2011; Pineles et al., 2010). There are no gender predilection as compared with adult where female is predominant (Finnis & Jayawant, 2011). The rate of spontaneous remission is higher in this group and the rate of generalisation is also lower, which reflects to its better prognosis (Pineles et al., 2010). Among all children with MG, 10-35% have symptoms limited to the ocular muscles (Castro, Derisavifard, Anderson, Greene, & Iannaccone, 2013). Unilateral or

bilateral ptosis is the most common presentation followed by strabismus, ocular movement limitation, lid twitch, orbicularis oculi weakness and amblyopia (Au et al., 2003; Kim, Hwang, Hwang, Kim, & Chae, 2003). During initial presentation, patients may present with ptosis only and developed strabismus within a few years later. Two Asian studies of childhood ocular MG showed that approximately 90% of patients presented initially with ptosis only, but at final follow up (1 to 14 years), up to 90% of patients developed concurrent strabismus (Kim et al., 2003; Kraithat, Hansapinyo, & Patikulsila, 2015). Although this may happen due to progression of MG, poor initial detection of strabismus is possible especially in younger children. Incomitant strabismus is more common than comitant strabismus (Kim et al., 2003). In both adult and juvenile MG, the most common extraocular muscle affected is the medial rectus and this was reported both in Asian and Western population (Smith & Lee, 2017). In contrast, Jong-Hyun Kim et al showed that exotropia with vertical heterotropia is the most common form of strabismus presented in South Korea followed by exotropia only and vertical heterotropia only (Kim et al., 2003). Ocular movement limitation occurred in 70% of children with ocular MG in their series but the ocular muscle limitation was found did not correspond with types of strabismus (Kim et al., 2003).

Ptosis and strabismus with pupil sparing can be confused with other neurological diagnosis. One differentiating feature of MG is variability of paretic muscle. Apart from fatigability, the variability of muscles affected is important for suspicion of MG. Variability of symptoms as seen in this girl is regarded as pathognomonic by some authority (Lin et al., 2017; VanderPluym et al., 2013).

High index of suspicion with good history taking and physical examination help physician to diagnose MG. The diagnosis is made based on clinical findings and it is supported by specific tests. Three common clinical tests to diagnose MG are fatigue test, sleep test and ice test (Smith & Lee, 2017). Fatigue test and ice test in particular hold high specificity, and a positive test is highly suggestive of MG (Kim et al., 2003; Luchanok & Kaminski, 2008). These tests are readily performed by an ophthalmologist in a clinic setting.

The other tests are categorized as serology, electrophysiology and pharmacology. In general, these tests are less sensitive in ocular MG and young children compared with generalised MG (Kim et al., 2003; Luchanok & Kaminski, 2008). Serology testing for AchR antibody has high specificity but low sensitivity (39 to 71%) in ocular MG compared with generalised MG (87 to 98%) (Lin et al., 2017). Positive AchR antibody is associated with generalisation in 24 to 35% of patient with ocular MG in 2 years (Lin et al., 2017). Although conversion to seronegative is associated with remission, AchR antibody is not used for monitoring because it may persist in circulation after remission (Anlar, Şenbil, Köse, & Değerliyurt, 2005). Muscle specific tyrosine kinase (Musk) antibody which usually associated with generalised, more severe presentation and poor response to therapy is rarely seen in ocular MG (S. H. Wong, Huda, Vincent, & Plant, 2014). Musk antibody is found in 40% of adult MG patients with seronegative to AchR antibody (Liew & Kang, 2013a; S. Wong, 2015). Tensilon or endrophonium test possess the highest sensitivity in diagnosing ocular MG. It has a sensitivity of 95% which is similar to generalised MG (Kraithat et al., 2015). This test uses short acting cholinesterase inhibitor injected intravenously. Positive result produces a rapid but transient improvement of clinical sign mostly

ptosis (Au et al., 2003; Kraithat et al., 2015). It is important to note the side effects of endrophonium, which includes bradycardia and arrhythmia. On the other hand, electrophysiological testing may show negative findings in about 50% of ocular MG in children (Kraithat et al., 2015). A specific procedure, which is single fiber electromyography, has higher sensitivity and specificity compared with other techniques (Liew & Kang, 2013a; Lin et al., 2017). Nevertheless, electrophysiological test is very technically challenging to perform on children and sedation or general anesthesia is usually required.

Apart from diagnostic tests, imaging modalities such as computed tomography and magnetic resonance imaging is selectively performed in patient with MG to detect enlarged thymus. Thymoma present in 10-15% of patients with MG and it is particularly high in seropositive MG and generalised MG (Mullaney, Vajsar, Smith, & Buncic, 2000). However, the presence of thymoma in children presented with ocular MG is rare, as reported in both Asian and Western studies (Liew & Kang, 2013b; Mullaney et al., 2000). Other important tests that usually performed are thyroid function test and thyroid antibodies due to its association with autoimmune thyroid disease (Au et al., 2003; Kanazawa et al., 2007).

In managing children with ocular MG, there are a few issues to consider. Children with MG especially in pre-pubertal group is known to have benign disease, less progression to generalised MG and have a good prognosis with higher rate of spontaneous remission as compared with adult MG. Therefore, careful judgment and good understanding of the disease may help to improve patient management. The goal of treatment for children with symptomatic ocular MG is initially to achieve best ocular function without causing harm and later to tackle cosmetic issue (Sanders et al., 2016). The treatment approach may involve non-medical, medical and surgical intervention. A non-medical approach such as prism correction glasses and patching to improve diplopia are normally applied simultaneously with medical treatment.

Medical treatment involves usage of medications such as pyridostigmine, steroid and even immunomodulatory agents. For children with symptomatic ocular MG, symptoms reliever such as pyridostigmine is considered as first line treatment in view of the tendency for the children to have spontaneous remission. The rationale of using pyridostigmine is to improve neuromuscular transmission of acetylcholine at the neuromuscular junction (Liew & Kang, 2013a; Sanders et al., 2016). Pyridostigmine is generally well tolerated in children and it was found to be beneficial to treat ptosis, but less effective for diplopia and motility deficiency, which is contrary with our patient (Liew & Kang, 2013a; Luchanok & Kaminski, 2008). Patient who presented with concurrent ptosis and strabismus were also less likely to respond to pyridostigmine (Liew & Kang, 2013a; Luchanok & Kaminski, 2008) In general, the improvement of symptoms with pyridostigmine in children with ocular MG is up to 94% (Castro et al., 2013; Liew & Kang, 2013b).

Immunosuppressive agents such as steroid or steroid sparing agent may be used as a second line treatment when trial of pyridostigmine failed to achieve treatment goals. Although steroid is rarely required in ocular MG, up to 80% of patients responded well to steroid especially for diplopia (Benatar, Sanders, Wolfe, McDermott, & Tawil, 2012; Kupersmith, 2009). Steroid increases synthesis of AChR and improves the organisation of junctional synaptic folds as

reported in an in vitro study (S. H. Wong et al., 2014). Apart from the therapeutic benefits, steroid is also found to reduce the incidence of generalised MG especially when the treatment is initiated early (Kupersmith, 2009; Luchanok & Kaminski, 2008). However, there is no strong randomize prospective study to support this. Steroid is also associated with dangerous adverse effects such as infection, growth deceleration, weight gain, bone demineralization and hyperglycemia (Pineles et al., 2010; Sanders et al., 2016). Therefore, before steroid treatment is initiated, a thorough and careful clinical judgment need to be made. Other immunomodulatory agents may be used to replace steroid. Although this is rarely indicated, azathioprine is usually chosen as the first choice followed by cyclosporine, mycophenolate mofetil, and tacrolimus (Sanders et al., 2016).

The role of thymectomy in children is unclear. In adult, elective removal of thymus in non-thymomatous MG is done to reduce the dose and duration of immunotherapy (Kraithat et al., 2015; Roberts et al., 2001). Pineles et al in their retrospective review of children with ocular MG concluded that thymectomy has a protective role against progression to generalised MG (Pineles et al., 2010). This has been supported by other case series (Kraithat et al., 2015). However, the International Consensus Guidance for Management of Myasthenia Gravis suggested that elective thymectomy should only be considered in generalised AChR positive MG that has poor response to pyridostigmine and immunosuppressive therapy (Sanders et al., 2016).

Amblyopia is common in children with ocular MG. Large angle strabismus and severe ptosis contributed to the development of amblyopia. Kim et al reported in their series, more than 20% of children were affected by amblyopia with almost all treated successfully with patching and occlusion therapy (Kim et al., 2003). A case series of 14 children with ocular MG in Thailand found 1 child developed amblyopia and despite adequate treatment the child vision remain poor at final follow up (Kraithat et al., 2015). They believed the key to successful amblyopia treatment is early detection and regular ophthalmic follow up.

Surgical intervention for strabismus and ptosis in children is rarely reported. In general, surgical intervention is performed when the functional limitation persists despite adequate treatment after symptoms stabilized for at least one year (Peragallo, Demer, Velez, & Pineles, 2013). In a retrospective review of 9 patients underwent strabismus surgery with adjustable sutures, 67% have a long term success rate (Peragallo et al., 2013). The mean preoperative ocular deviation in the series were 40.5 ± 32.5 prism diopters for horizontal and 25.6 ± 36.7 prism diopters for vertical (Peragallo et al., 2013). They also reported that strabismus surgery was less effective in older patient with generalised MG as well as in long standing ocular deviation where muscle contracture already developed. Strabismus surgery is believed to be successful in adult because of intact fusional component of stereopsis. In younger children where fusion and other visual component is still developing, a successful surgery is uncertain. Nevertheless, a case report by Ellenhorn et al published in 1986 showed a successful correction of amblyopia in a 5 year old child after patching therapy and strabismus correction surgery (Ellenhorn, Lucchese, & Greenwald, 1986).

Residual or persistent ptosis occur in 46-66% of children with ocular MG although the ptosis is rarely clinically significant (Pineles et al., 2010). Nonetheless, ptosis surgery in ocular MG is

still being performed for certain functional reason. External levator advancement, frontalis slings and tarsomyectomy are the procedures performed. As the aim of surgery is not aesthetic, undercorrection of ptosis is normally practiced to avoid complications such as lagopthalmos and exposure keratopathy (Bradley, Bartley, Chapman, & Waller, 2001; Litwin et al., 2015). Litwin et al in their review of 23 patients underwent ptosis correction surgery showed 87% of ptosis were corrected after one procedure at the final follow up of 29 months (Litwin et al., 2015). Seventeen percent of the patients needed to undergo second procedure because the first operation was complicated with exposure keratopathy (Litwin et al., 2015). Other complications that may be associated with ptosis surgery are worsened diplopia and recurrent ptosis (Bradley et al., 2001; Litwin et al., 2015).

4.0 Summary

In summary, children with autoimmune ocular MG especially in pre-pubertal age group has a benign course of disease with better prognosis. Blood investigation to detect AChR antibody has low sensitivity but essential to rule out congenital type of MG which has different etiology. Endrophonium test is more superior to single fiber EMG in establishing diagnosis of ocular MG in children. There is no single randomized clinical trials to compare mode of treatment in patient with MG in general. For children, the rate of spontaneous remission is higher compare to adult. Generally, pyridostigmine should be considered as a first line treatment as it acts as symptomatic relief. Steroid is associated with severe side effects in children and should be avoided unless strongly indicated. Surgical removal of thymus gland in elective setting is controversial as rate of progression to generalised MG in children is low. Children who presented with large angle strabismus and severe ptosis should be seen frequently by ophthalmologist to detect amblyopia at early stage. Occlusion and patching therapy initiated during early detection of amblyopia can prevent long-term visual deficit. Strabismus and ptosis surgery is rarely done in children. However early stabilization of symptoms may give an option for correction which may help in preventing amblyopia.

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Declaration

The authors declare no conflict of interests. The authors alone are responsible for the content and writing of the paper.

Authors' contribution

Author 1: Wrote the manuscript with consultation from author 2 and 3
Author 2: Provided critical feedback
Author 3: Wrote the manuscript, provided critical feedback and supervised the whole process.

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