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Mini Review

Juvenile Myasthenia Gravis: A Short Review

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Abstract

Juvenile myasthenia gravis (JMG) is an autoimmune disorder of neuromuscular transmission caused by production of antibodies against components of the postsynaptic membrane of the neuromuscular junction. The patients present with a wide range of symptoms-from isolated intermittent ocular symptoms to general muscle weakness with or without respiratory insufficiency. Prepubertal children in particular have a higher prevalence of isolated ocular symptoms, lower frequency of acetylcholine receptor antibodies, and a higher probability of achieving remission. It must be differentiated from congenital myasthenia which is a channelopathy rather than autoimmune disease. Treatment commonly includes anticholinesterases, corticosteroids with or without steroid-sparing agents, and newer immune modulating agents. Plasma exchange and intravenous immunoglobulin (IVIG) are effective in preparation for surgery and in treatment of myasthenic crisis.

Keywords: Myasthenia; Ptosis; Pyridostigmine

Abbreviations: JMG: Juvenile Myasthenia Gravis; IVIG: Intravenous Immunoglobulin; MG: Myasthenia Gravis; Ab: Antibodies; AChR: Acetylcholine Receptor; MuSK: Muscle-Specific Kinase; LRP4: Leucine Rich Protein 4; RNS: Repetitive Stimulation Test; SFEMG: Single Fiber Electromyography; CT: Computed Tomography; MRI: Magnetic Resonance Imaging

Introduction

The first description of myasthenia gravis (MG) with onset in childhood originates from Erb in 1879 [1]. The definition of juvenile myasthenia gravis (JMG) includes infants, children, and adolescents aged 0 to 19 years [2]. JMG patients are subdivided according to the occurrence of the first symptoms as prepubertal (first symptoms before the age of 12 years) and postpubertal (first symptoms after the age of 12 years) [3]. The main action of disease is production of antibodies (Ab) against the components of postsynaptic membrane, predominantly the binding acetylcholine receptor (AChR). MG is divided into five groups: ocular myasthenia (grade I), mild (grade IIa), moderate (grade IIb), severe weakness other than ocular (grade III), and very severe weakness defined by intubation with or without mechanical ventilation (grade IV) [4]. It is a rare disorder of the childhood which accounts for less than 10-15% with an incidence of 1-5 per million per year [2].

In Asian population, up to 50% of MG patients present with the first symptoms in childhood (age peak between 5 and 10 years); no difference in sex distribution has been observed. In this population, more than 70% of cases are restricted to ocular symptoms and benign course is common [2,5]. In post-pubertal children, the clinical course is similar to adult-onset MG. The patients frequently present with ocular symptoms at the onset; generalized-muscle weakness develops in up to 80% in the course of the disease [2].

Pathogenesis: In the majority of cases MG is caused by antibodies to the nicotinic acetylcholine receptor (AChR) which is found in over 80% adults with generalised disease but only in 55% of adults with weakness confined to the oculomotor muscles. Patients with AChR antibodies are often referred to as seropositive. AChR antibodies are probably less frequent in prepubertal patients than in adolescent and adult patients [6]. Antibodies to muscle-specific kinase (MuSK) and to Leucine rich protein 4 (LRP4) have been reported in some seronegative patients.

Clinical Features: A typical clinical symptom of abnormal neuromuscular transmission is a fatigability that occurs acute or subacute. The first symptoms may develop as early as in the first year of life [7]. Generally, the developmental milestones are normal before disease onset. Clinical presentation depends on the muscle group affected: ocular problems such as ptosis or ophthalmoplegia,

bulbar muscle weakness, respiratory muscle involvement, and proximal symmetrical muscle weakness. Ocular symptoms are common at onset. The definition of ocular MG is restricted to the ocular symptoms for 2 years without becoming generalized [8]. Ptosis usually aggravates after physical activity. It may be unilateral or bilateral. Children may complain about double vision. Sometimes, children may present having difficulties in climbing stairs because of diplopia. About 50% of children with ocular symptoms develop systemic or bulbar muscle involvement within 2 years after onset. If bulbar muscles are involved there will be nasal regurgitation. Symptoms depend upon weakness.

When generalized muscle weakness is there, patients have problems to walk a normal distance or to run, have difficulties in climbing stairs or to rise from a squatting position. In many conditions generalized muscle weakness, which presents as painless fatigability of the bulbar and limb musculature, with dysphonia, dysphagia, and proximal limb weakness. Children are at risk of choking or aspiration and are at increased risk of chest infection. Occasionally, impairment of the respiratory muscles necessitates ventilatory support. This is known as "myasthenic crisis". In the physical examination, children may appear normal if examined after rest; repetitive assessment of muscle strength with standardized tests is recommended [9]. Transient neonatal myasthenia is a condition that results from transfer of maternal AChR antibodies across the placenta leading to defects of neuromuscular transmission in the neonate [10]. Not all mothers have detectable AChR antibodies and a few are asymptomatic at the time. Usually the affected baby is normal at birth, subsequently developing signs such as hypotonia, weak cry, poor suck, reduced movements, ptosis and facial weakness, and occasional respiratory insufficiency requiring mechanical ventilation. Short-term treatment with anticholinesterases is usually sufficient.

Diagnosis: (Table 1)

Table 1: Diagnostic modalities of myasthenia gravis.

Diagnostic Modality [3]	Specific tests	Importance
Physiological tests	Sleep test	After having the baseline deficit documented (measurements of ptosis, motility disturbance), the patient rests quietly with eyes closed for 30 minutes. The measurements are repeated immediately after the patient "wakes up" and opens his or her eyes. Improvement after rest is highly suggestive of MG.
	Ice pack test	The ice-pack test is often helpful for diagnosing patients, but only if they have ptosis. An ice pack is placed over lightly closed eyes for 2 minutes. Improvement of ptosis occurs in most patients with MG
Serology	AchR Antibody	Detection of antibodies to the AChR supports the diagnosis of JMG. Some of seronegative children who are negative for AChR antibodies will have "low affinity" antibodies to the AChR which were not detectable using the standard assays
	Musk Antibody	Some MG patients without AChR antibodies are found to have antibodies against muscle-specific kinase (MuSK). MuSK positive MG is rare in children, and these children represent a distinct subgroup of JMG, 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 [11].
	LRP4 Antibody	Very low number of seronegative JMG patient turn out to be positive for Lrp4-Ab [12].
Pharmacological	Edrophonium test	Tensilon test involves intravenous infusion of edrophonium. The patient is observed, and ideally a video recorded, looking for a transient improvement in previously documented weakness, for example, ptosis, dysphonia.
	Neostigmine test	This test is particularly useful in patients who may require a longer observation period for accurate ocular alignment measurements than that allowed by edrophonium. A positive test produces resolution of signs within 30-45 minutes.
Electrophysiology	RNST	Repetitive stimulation test (RNS), usually with low frequency of 3 Hz. In case of a pathological decrement response (decline from the first to the fifth amplitude more than 10%), the result is very suggestive of a transmission defect.
	SF-EMG	Single fiber electromyography (SFEMG) is more sensitive than RNSs and can provide pathological results in patients with normal decrement response in RNSs.
Imaging		Before the steroid therapy, both subcutaneous testing and chest X-ray should be performed to exclude fluent tuberculosis. Computed tomography (CT) or magnetic resonance imaging (MRI) of the chest to check for thymus hyperplasia or thymoma are needed.

Treatment: (Table 2)

Table 2: Treatment modalities.

Clinical Subtype	First line Therapy	Additional Therapy	
Ocular myasthenia	Pyridostigmine [13]	Short term steroid therapy	-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, maximal 300 mg/d. -In older children/adults, the maximum starting dose is 60 mg 3 to 4 times daily and absolute maximum recommended dose in adults is 120 mg every 3 hours during the daytime
Generalized myasthenia [13-15]	Pyridostigmine + Steroids	long-term immunosuppressants thymectomy Azathioprine (Usually used in combination with corticosteroids Occasionally used alone) Cyclosporin A Cyclophosphamide MMF Rituximab	-Prednisone and prednisolone are the first-line therapy in children with persisting symptoms. The starting dosage is 0.5 to 1 mg/kg (maximum 30 mg/d), with a possible increase up to 2 mg/kg/d (maximum 60-80 mg/d). -Recommended initial dose of azathioprine is 0.5 to 1mg/d; increase of 0.5mg/kg/d every 4weeks up to 2.5 mg/kg/d (maximum 150-200mg/d) in two divided doses is possible.
Myasthenia crisis	Pyridostigmine +Steroids +Plasmapheresis/IVIg	long-term immunosuppressants thymectomy	The standard dose of IVIg has been 2 g/kg administrated over the period of 2 to 5 days, maximum dose 150 g. This regimen can be repeated every 4 to 8 weeks in patients who have failed to respond to other therapies.

Conclusion

JMG is one of the subtypes of MG with very good prognosis and outcome. It has more ocular predominance then adult MG. Diagnosis is done by both serological and electrophysiological tests. Pyridostigmine is the primary modality of management. Early diagnosis and management can save many patients from acute crisis. To some extent, treatment options for adults may be adapted for children, but specific pathophysiology differences must be considered in this population group.

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