

## MYASTHENIA GRAVIS IN PEDIATRICS

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### Abstract

Myasthenia Gravis is a chronic autoimmune neuromuscular disorder characterized by abnormal fatigability of muscle after repeated or sustained activity and improvement after rest. Peak incidence is seen in young adults but it may also occur in infancy and childhood. Three separate entities are characteristic in childhood period (a) transient neonatal myasthenia in an infant of myasthenic mother, (b) congenital or infantile myasthenia in an infant of non-myasthenic mother and (c) juvenile myasthenia similar to adult myasthenia.

The author focuses on the neuroimmunological mechanism, clinical features, laboratory and electrodiagnostic testing.

**Keywords:** Myasthenia Gravis, Child, Congenital, Neuroimmunology.

Myasthenia gravis (MG) is an autoimmune disorder that affects the neuromuscular junction at the postsynaptic level (1).

The neuromuscular transmission efficacy will be readily blocked, due to the morphological changes in the neuromuscular junction which could cause an increased diffusion of acetylcholine from the synaptic cleft, by reducing the ability of acetylcholine to interact with the functional receptors. Most of the acetylcholine molecules delivered in the synaptic terminal by an action potential will be faster hydrolyzed by acetylcholinesterase.

### Physiological abnormality in Myasthenia Gravis

The pathophysiology of MG is nearly well understood today. The main mechanism is generated by sensitized T-helper cells and an immunoglobulin antibody (IgG) – directed attack on the nicotinic acetylcholine receptor of the neuromuscular junction.

Acetylcholine receptor antibodies are present in most patients with Myasthenia Gravis, but they are not the only ones.

Acetylcholine receptors antibodies can be transferred passively to animals producing experimental autoimmune myasthenia gravis. The physiopathological features of myasthenia are described by a diminished numbers of acetylcholine receptors that are disposed on the muscular postsynaptic membrane (2). The postsynaptic folds are flattening or “simplified”. These abnormalities cause a defective efficiency of the neuromuscular transmission. Antibody binds to the  $\alpha$ - subunit of the acetylcholine receptor, because this subunit is also called the main immunogenic region. Removal of acetylcholine receptors (by plasmapheresis) leads to recovery.

Animals immunized with an acetylcholine receptor (purified extract from *Torpedo Californica*) will begin to produce acetylcholine receptor antibodies, which can develop an autoimmune disease experimental induced.

### Clinical manifestations of Myasthenia

Being the most common disorder of the neuromuscular junction, involving also a defective neuromuscular transmission, the degree and the variations of muscle weakness are located in ocular, bulbar, limb and respiratory muscles. In child, the muscular deficit occurs frequently at bulbar and respiratory level. According with the clinical course of the disease myasthenia gravis could be: generalized, ocular and with bulbar involvement. The immunitary attack is directed at proteins in the postsynaptic membrane of the myoneural junction, reason for why, sometimes myasthenia is accompanied by a myophatic episode that could be transitory or prolonged. The changes in the topography of muscular deficit depend by the muscle group affected, and for the clinician is also important to establish the motor deficit trough so called Myasthenic score. Due to the fact that the disorder is limited to the neuromuscular junction, no abnormality of cognition, sensory function or automatic function is incriminated.

### Particularities regarding the neonates and children with myasthenia

About 15% of children are born from mothers with myasthenia and due to the transplacentally passing of IgG antibodies some of them have generalized weakness. This clinical aspect can happen to MuSK- positive myasthenia gravis and with seronegative mothers. Nevertheless no respiratory distress may present at birth, generalized muscle weakness and difficulties bin suckling could be a signal alarm. These symptoms tend to improve spontaneously in 2-3 weeks. Exceptionally, Mestinon and plasma exchange could be used. In neonates with congenital myasthenic syndrome which also is clinically manifest at birth, a differential diagnosis should be performed. A false friend could be the syndrome of floppy infant. Arthrogryposis multiplex congenital occurs in rare cases.

Children have usual antibody-mediated myasthenia, easy to diagnose if antibodies anti acetylcholine receptors or MuSK are present. We must have in our attention that an antibody-negative test could indicate a late onset congenital disease.

### Immunogenetics of myasthenia

In myasthenia, class II molecules of the major histocompatibility complex (MHC) are expressed on the antigen presenting cell, in this way, the T cells become reactive against the acetylcholine receptor. The MHC class II is very important in determining the susceptibility. Patients with myasthenia gravis have the histocompatibility subtypes DR3 and DQ2. The HLA system is involved by HLA –B8 and HLA-DR3 antigens. C3, C4 complement system polymorphisms could be depended by the circulating acetylcholine receptors and immune circulating complexes.

### Immunoserological investigations

Certain studies should be performed to exclude other disorders that could interfere with myasthenic symptoms. Laboratory tests for Myasthenia Gravis are more specific from serologically point of investigation. The following studies should be performed:

Antibody tests: Anti –AChR antibodies, Anti-MuSK antibodies, Antistriated muscle antibodies, Antinuclear antibodies, Anti –ds-DNA antibodies, Anti-Jo 1 antibodies, Anti-Smith antibodies, Immune circulating complexes, Immunogram, C3, C4 complement compounds.

Hematology: Complete blood cells count.  
Biochemistry: Liver and renal profiles, rheumatoid factor, electrolyte panel.

Endocrine serological markers: Thyroid –stimulating hormone (TSH), Triiodothyronine (T3), Thyroxine (T4).

### Electrodiagnostic

In clinical practice, the pathological features of neuromuscular transmission in myasthenia can be performed by electromyography. This electrophysiological technique involves nerve conduction activity, diagnosed by repetitive nerve stimulation (RNS) and single fiber electromyography (SFEMG). In myasthenia gravis a decrement greater than 10% is characteristic. Regarding the single fiber electromyography, when jitter is present on the electromyographic route, could be a certain sign of myasthenia, although for 80% of the patients could not be specific.

In Child, Myasthenia represents about 10% from the total sum of clinical cases of disturbances of the synaptic transmission at the level of neuromuscular junction. 75% of cases appears between 10 and 15 years of age. In pediatrics practice Myasthenia Gravis is described by four clinical types: (a) Transient neonatal myasthenia, (b) Persistent neonatal myasthenia, (c) Juvenile myasthenia, (d). Congenital and familial myasthenic syndromes. Autoimmune myasthenia gravis (MG) encompasses all of the immunologically-mediated disorders affecting the endplate region of the postsynaptic neuromuscular junction. Nearly all of these disorders involve a loss of immunological self-tolerance, though transitory neonatal MG is a self-limited disorder that follows passive transfer of maternal antibodies to the fetus (3, 4).

### *Transient neonatal myasthenia*

Occur at approximately 10-15% of new born from myasthenic mothers. This clinical manifestation is the consequence of the transfer of maternal antibodies through placenta, in the fetal circulation (4). The presence of acetylcholine antibodies at mothers and fetus was proved through serological investigations. It is still unknown why some of the new born of myasthenic mothers develop a transient neonatal myasthenia

Clinical features: The symptoms make them first appearance precocious. In the first 48 hours of life is find out an important hypotonia, poor or weak suck, weak scream, and sometimes respiratory distress. Palpebral ptosis is present only in a reduced percent of the cases. The symptoms can persist from some days of neonatal life, at 4-6 weeks (5). The course of the symptoms is leading to a remission of them once with acetylcholine antibody depletion or disparition.

### *Persistent neonatal myasthenia*

The symptoms are like in transient neonatal myasthenia form. Mother don't have myasthenia, but at least of a relatives can be affected. The disease persist the whole life. The eyelids and the ocular muscles are severe involved.

### *Juvenile Myasthenia*

Is a rare disease in children. Clinically it usually occurs after ten years of age with palpebral ptosis and diplopia. The intercostal and facial muscles are frequently affected. It is characterized by the improvement after rest and exacerbation through repeated movements. The "myasthenic crisis" occur in inter-current infections or certain state of stress being a hasten exacerbation which menace the life.

### *Familial and Congenital myasthenic syndromes*

These genetic features of Myasthenia Gravis are not imunologically mediated, being the expression of different abnormalities of the synaptic neuromuscular transmission. Most of them are autosomal recessive inherited (6). Depending by the site of the abnormality, and by the neuromuscular transmission, the myasthenic congenital syndromes are divided in: presynaptic defects –abnormality in resynthesis and storage of the acetylcholine plus a reduced number of synaptic vesicles and impaired release of acetylcholine – and postsynaptic defects –decreased number in acetylcholine receptors, abnormality in binding affinity, prolonged opening time of acetylcholine channels with clinical features like slow channel syndrome and fast channel syndrome. The clinical evolution is heterogeneous. In near 2% of cases the symptoms the symptoms appears from birth or can be present in the first two years of infancy. Sometimes could exist an anamnesis of diminished fetal movements, in this case the clinical debut of the disease being prenatal (arthrogryposis /arthrogryposis multiplex congenital).

The postsynaptic defects, generally show a moderate symptomatology, in this area being involved Congenital Myasthenia Gravis too. Grace to the histopathological

examination through immunofluorescence it was described a deposition of IgG and complement at the level of neuromuscular junction.

Familial Myasthenia, represent the clinical prototype of a synaptic defect, abnormality in acetylcholine storage and resynthesis being essential. The beginning of the disease can be noted from birth with variable hypotonia, sometimes severe, in contrast with extraocular motricity which is usually normal although a degree of facial muscle affection can also exist.

The course of the disease is characterized by repeated episodes of muscle weakness sometimes apnea or neonatal respiratory distress that are life menacing. These episodes could be present end long to suckling period and in childhood rarely in adult life.

The congenital and familial myasthenic syndromes are immunohistochemically differentiated depending by the proteins that cause the mutations into acetylcholine receptor subunits.

#### Thymectomy and ocular myasthenia gravis in child

In the research literature is already specified that the disease will progress in about 50% of patients with initial ocular myasthenia gravis (7). Ocular myasthenia gravis in child is less common, but not the same thing happens with ocular onset of the disease. Thymectomy is generally considered the long term surgical therapy with good results in generalized myasthenia gravis. Regarding the ocular myasthenia gravis in child and benefits of thymectomy, the best improvement makes felt his presence if the children are thymectomized on early after the onset of the disease.

#### The usage of intravenous immunoglobulin

Venous access in child is a little beat disputable regarding the infusion with immunoglobulins. Its effectiveness has been disputable too with variable acetylcholine receptor antibody responses. Children should be assessed after treatment, heaving in view that a high dosage of immunoglobulin infused doesn't mean a quick clinical improvement and could influence in a bad way the turnover of acetylcholine receptor. The adequate treatment scheme for children with regards of intravenous immunoglobulin administration is about 2mg/kg body weight infused at variable rates of 2 g/kg for one day, 0,66 g/kg daily for three days, and 0,5 g/kg daily for four days. The therapy should gradually institute. Concluding with this, in one patient the total dose should be about 0,8 g/kg adjusted to body weight. Usually, the children shows a good tolerance when treatment is applied. An important remark is

to mention that in some cases after intravenous immunoglobulin administration, a decrease in anti AChR antibody levels could be observed, despite that a correlation between clinical response to therapy and antibody titers, doesn't exist. The addressability and specificity of intravenous immunoglobulin therapy aimed especially in juvenile myasthenia gravis, myasthenic crisis and the patient preparation for surgery, but unfortunately offers a limited long-term benefit.

#### Myasthenic crisis

A serious complication of myasthenia gravis is respiratory failure. According to Drachman (8), this may be secondary to an exacerbation of myasthenia (myasthenia crisis) or to treatment with excess doses of a cholinesterase inhibitor (cholinergic crisis). Managing respiratory failure and differentiating a myasthenia from a cholinergic crisis is reviewed. Due to the unpredictable appearance of respiratory failure, hospitalization is recommended for most children with exacerbations or complications of myasthenia gravis. Anticholinesterase therapy and specific antibiotherapy, should be properly conducted, the separation from mechanical ventilator support being extremely vital in the course of the disease and clinical improvement(9)

#### Conclusions and discussions

Myasthenia gravis is diagnosed in children via blood tests, a drug test that challenges the muscle weakness, which is positive if strength improves, and muscle fatigability tests by observing a child doing repetitive movements which bring about weakness. It can be treated with medications to upgrade chemical messages in the neuromuscular junction, and medications to dampen down the immune response, removal of the thymus gland that is important in childhood immunity, and cleaning the blood of antibodies via plasmapheresis. Occasionally the condition can spontaneously resolve, but there is no cure. It can become fatal if the muscles controlling breathing are involved, but the majority of cases are well maintained on medication.

The purpose of this review article was to bring a short and better understanding of pediatricians, neurologists and general practitioner medicine in the front of a clinical cases as regards the clinical manifestations of Myasthenia Gravis in pediatrics. The pediatric neurologist and family physician should play an important role in the diagnosis and management of children with Myasthenia Gravis. Laboratory testing and an autoimmune evaluation of the disease are addressed to general immunologist or neuroimmunologist too.

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