Childhood Myasthenic Disorders

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of Master Degree in Neuropsychiatry
By

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List of Abbreviations

3&4-DAP	3&4 Diaminopyridine
Ach	Acetylcholine
Ach.BP	Acetylcholine binding protein
AchE	Acetylcholine esterase
Achn	Acetylcholine neurotransmitter
AchR	Acetylcholine receptors
AD	Autosomal dominant
ADPEO	Autosomal dominant progressive external Ophthaloplegia
ANT1	Adenine nucleotide transporter 1 gene
AR	Autosomal recessive
ARIA	Acetylcholine receptor inducing activity
ATP	Adenosine triphosphate
BGT	Bungarotoxin
Ca	Calcium
CAG	Codes for the amino acid glutamine
CAMP	Compound muscle action potential
CHAT	Choline acetyl transferase
CHRNA	Cholinergic receptor nicotinic A
CK	Creatine kinase
CMS	Congenital myasthenic syndromes
CMS.EA	Congenital myasthenic syndrome episodic apnea
COLQ	Collagenic tail peptide Q

Cos cells	Cells being **C**V-1 in **O**rigin, and carrying the **S**V40 genetic material
CPEO	Chronic progressive external ophthalmoplegia
CT	Computerized tomography
CTG	Cardiotocography
DMPK	Drug metabolism and pharmacokinetics
DOK7	Docking protein -7
EMG	Electromyography
ENMC	European neuromuscular center
EP	Endplate
EPP	Endplate potential
FCCMS	Fast channel congenital myasthenic syndrome
HZ	Hertz
JMG	Juvenile myasthenia gravis
K	Potassium
LAMB2	Laminin beta 2 subunit
LES	Lambert-Eaton syndrome
LRP4	Low density lipoprotein receptor-related protein 4
MASC	Myotube-associated specificity coponent
MEPC	Microemulsion pre-concentrate
MEPP	Miniature endplate potential
MG	Myasthenia gravis
MUSK	Muscle-specific kinase
Na	Sodium
NAP25	Nucleic acid probe 25
NMJ	Neuromuscular junction
NO	Nitric oxide
NOS	Nitric oxide synthase
NSF	N-ethyl moleimide sensitive factor

OMG	Ocular myasthenia gravis
PLEC1	Plectin
POLG	Polymerase gamma gene
RAPSYN	Receptor associated protein of synapse
SBMA	Spinal and bulbar muscular atrophy
SCCMS	Slow channel congenital myasthenic syndrome
SCN4A	Sodium channel
SFEMG	Senslefiber electromyography
SMN1	Survival of motor neuron 1 gene
SNAP25	Synaptic vesicle associated protein 25
SNMG	Seronegative myasthenia gravis
UTR	Untranslated region

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Introduction

Disease processes affecting the neuromuscular junction (NMJ) are relatively common. The most common cause is acquired, autoimmune myasthenia gravis. A less common but important group of inherited congenital disorders of the neuromuscular junction are the congenital myasthenic syndromes (**Engel et al., 2003**).

Types of childhood myasthenic disorders are neonatal (transient) myasthenia gravis, congenital myasthenic syndromes and autoimmune juvenile myasthenia gravis (**singh, 2010).**

Transient neonatal myasthenia gravis (TNM) as a result of the placental transfer of maternal acetyl choline receptors (ACHR) antibodies affects approximately 10% of infants born to mothers with autoimmune myasthenia gravis (**Tellez-Zenteno et al., 2004).**

Childhood autoimmune myasthenia gravis is caused by autoantibodies that bind to and reduce the number of acetyl choline receptors at the postsynaptic membrane. Autoimmune myasthenia gravis is considered to be the prototypical synaptic disorders (**Andrwes et al., 1994**).

Autoimmune myasthenia gravis is an acquired disease with a genetic basis, which is related to human leukocyte antigen (HLA)-B8 and DR3 which is present in approximately 60% of Caucasians. The initial symptoms of childhood autoimmune myasthenia gravis are seen after 12 months of age and more common in females. The initial presentation is with diplopia caused by asymmetrical ophthalmoplegia, ptosis is frequently present. In the generalized form painless fatiguability of the bulbar and limb musculature follows at a variable rate, with resultant dysphonia, dysphagia and proximal limb weakness. Occasionally impairement of respiratory muscles requires ventilatory support. In some individuals, symptoms and signs of weakness remain confined to the extraoccular muscles (ocular myasthenia) (**Andrwes et al., 1994, Vincent et al., 2004**).

However, 80% of individuals with an ocular presentation develop generalized muscle weakness within 2 years **(Evoli et al., 1998**)

Treatment of juvenile myasthenia gravis includes medications, thymectomy, intravenous immunoglobulin and plasma exchange. In most cases medications are the first line of treatment, medications include oral anticholine esterase agents, and corticosteroids. (**Evoli et al., 1998**).

Congenital myasthenic syndromes are genetic disorders of neuromuscular transmission. They are associated with mutations in a series of different proteins that are either directly involved in signal transmission or involved in the formation and maintenance of synaptic structure (**Engel et al., 2010).**

The effect of the disease is similar to lambert-eton syndrome and myasthenia gravis, the difference being that congenital myasthenic syndromes (CMS) are not autoimmune disorders (**Banwell at al., 2004**).

Congenital myasthenic syndromes are hereditary diseases. More than eleven different mutations have been identified and the inheritance pattern is typically autosomal recessive (**Barisic et al., 2005).**

The types of congenital myasthenic disorders are classified into three categories presynaptic, postsynaptic and synaptic. Postsynaptic defects are the most frequent cause of congenital myasthenic syndromes and often result in abnormalities in the acetyl choline receptors. In the neuromuscular junction there is a vital pathway that maintains synaptic structure and results in aggregation and localization of acetyl choline receptors on the postsynaptic folds. This pathway consists of agrin, muscle specific tyrosine kinase (MuSK), acetyl choline receptors and

the receptor association protein of the synapse (RAPSN). The most majority of mutaions causing congenital myasthenic syndromes are found in the acetyl choline receptors (ACHR) subunits and receptors association protein of synapse (RAPSN) Most of the mutations of the acetyl choline receptor are mutations of the cholinergic receptor nicotinic epsilon (CHRNE) gene. Most of mutations are autosomal recessive (**Abicht et al., 2012).**

Presynaptic symptoms include brief stop of breathing, weakness of the eye, mouth and throat muscles. These symptoms often result in double vision and difficulty in chewing and swallowing. Postsynaptic symptoms in infants include severe muscle weakness, feeding and respiratory problems, and delays in the ability to sit, crawl and walk. Onset symptoms for all ages may include droopy eyelids. Synaptic symptoms include early childhood feeding and respiratory problems, reduced mobility, motor milestones (**Singh, 2010).**

Therapeutic agents used in treatment of congenital myasthenic syndromes include acetylcholinesterase inhibitors, 3,4 diaminopyridine (3,4 DAP), quinidine sulphate, fluoxetine, acetazolamide and ephedrine (**Engel and Sine,2005, Besson et al., 2006).**

A form of presynaptic congenital myasthenic syndrome is caused by an insufficient release of acetylcholine and is treated with cholinesterase inhibitors. Postsynaptic fast channel congenital myasthenic syndrome is treated with cholinesterase inhibitors and 3,4 diaminopyridine. Postsynaptic slow channel congenital myasthenic syndrome is treated with quinidine or fluoxetine. Ephedrine has been tested on patients in clinical trials and appears to be an effective treatment for docking protein-7 (DOK7) congenital myasthenic syndrome. Ephedrine also known as oral salbutamol, can lead to a profound improvement in muscle strength (**Palac, 2012).**

Aim of the work

The aim of the study is to review childhood myasthenic disorders in order to help proper diagnosis and to elucidate the recent updates in treatment of such disorders.