The History of Myasthenia Gravis

In 1672 Thomas Willis published a book, “De anima brutorum” in which he wrote about “a woman who temporarily lost her power of speech and became mute as a fish” [1]. This has been interpreted as being the first written description of myasthenia gravis (MG). Others give credit to Wilks for the first report of disease in 1877, characterized as a bulbar palsy without anatomic lesion [2]. The first reasonably complete accounts were those of Erb in 1878 and Goldflam in 1893 [3, 4] and for many years thereafter, the disorder was referred to as the Erb-Goldflam syndrome. Jolly was the first to use the name myasthenia gravis in 1895 and to demonstrate the “myasthenic reaction” of muscle repeatedly stimulated by Faradism [5], introducing the basic criteria of instrumental techniques of MG diagnosis, the repetitive nerve stimulation, elaborated later by Desmedt [6].

The beneficial effect of physostigmine on myasthenic symptoms was discovered in 1934 by Mary Walker, who supposed also that the neuromuscular junctions (NMJ) were the focus of the disease [7]. Dale, Nobel Prize winner of 1936, showed acetylcholine (ACh) as neurotransmitter at the NMJ and the anticholinesterase activity of physostigmine [8]. The association of MG with thymic tumors and hyperplasia was recognized in 1901 by Carl Weigert, who described a myasthenic patient with a thymic mass [9] and in 1911 the first thymectomy was carried out by Sauerbruch in a female MG patient [10]. In 1949 Castleman and Norris reported a series of patients with thymic hyperplasia and thymoma related to MG [11].

The autoimmune nature of MG was defined by Patrick, Lindstrom, Fambrough, and Lennon in the early 1970s [12-14]. Research later showed the presence of ACh-receptor (AChR) antibodies in serum of patients affected by MG and the production of CD4+ and CD8+ cells in cases with thymomas [15].

The Epidemiology of Myasthenia Gravis

MG is an uncommon disease; estimated annual incidence is 2.5 to 20 per million. Prevalence is 50 to 400 cases per million, higher above 40 years. Lifetime risk is 500 per million. The female-to-male ratio is said classically to be 6:4, but as the population has aged, the incidence is now equal in males and females [16]. MG presents at any age, with a bimodal pattern of onset: female incidence peaks in the third decade of life, whereas male incidence peaks in the sixth or seventh decade. Mean age of onset is 28 years in females and 42 years in males. Transient neonatal MG occurs in infants of myasthenic mothers who acquire receptor antibodies via placental transfer of IgG. Some of these infants may suffer from transient neonatal myasthenia due to effects of these antibodies. Rare, nonimmune mediated forms, collectively referred to as congenital MG, may be the result of mutations that adversely affect neuromuscular transmission. Recent advances in treatment and care of critically ill patients have resulted in marked decrease in the mortality rate. The rate is now 3-4%, with principal risk factors being age older than 40 years, short history of severe disease, and thymoma. Previously, the mortality rate was as high as 30-40%.

The Pathophysiology of Myasthenia Gravis

ACh Receptor Structure

AChRs are located at peak of muscular synaptic folds. Their concentration is 10,000 per μm². The nicotinic AChRs consist of five polypeptide subunits clustered around the central receptor channel. Nine α subunits have been cloned, along with four β subunits. In the NMJ, δ and γ subunits also have been identified. The γ subunit is replaced by an ε subunit in the adult muscle. In adult skeletal muscle there are α1, α1, β1, δ, and ε subunits, in fetal muscle α1, α1, β1, δ, and γ. In
extraocular muscles, some fibers contain both adult and fetal AChRs. The amino acid sequence for the \( \alpha \) subunits consists of a glycolipid region (which contains the ACh binding site and a sulphhydryl groups) with four hydrophobic regions that span the membrane.

The ACh binding site is a dimer formed by 3 or more peptide loops on the \( \alpha \) subunit (principal component) and 2 loops on the adjacent subunit (complementary component). Their activity is binding to both sites needed for the channel to open and binding to only one site to prevent channel activation. The main immunogenic region of the AChR is the extracellular N-terminal of the poly peptide component in the \( \alpha 1 \) subunit. Structural proteins clustered at NMJs (rapsyn) and the muscle-Specific Kinase (MuSK) receptor (receptor tyrosine kinase) are involved in MG-AChR antibodies negative and in congenital MG. Other muscle membrane structural proteins are involved in different autoimmunological disorders and muscular structural pathologies (muscular dystrophies).

**ACh Receptor Physiology**

Nicotinic receptors are found in a variety of tissues, including the autonomic nervous system, the neuromuscular junction, and the brain of vertebrates. The high quantities of receptors in these tissues and the use of neurotoxins from snake venom (e.g., cobra venom) that bind specifically to the nicotinic receptor aided the purification of the receptor protein. Agonists such as ACh, carbachol, nicotine produce the physiological responses associated with nicotinic cholinergic activation. ACh produces an influx of sodium through a ligand-gated ion channel. ACh and carbachol also stimulate muscarinic receptors and therefore should be considered mixed cholinergic agonists. Alpha-Bungarotoxin binds to the \( \alpha \) and \( \beta \) subunits and probably blocks both the channel and the acetylcholine binding site. Local anesthetics and other compounds such as phencyclidine bind to the receptor, apparently at the site of the sodium channel and modulate the binding of acetylcholine to the active site. Local anesthetics also prevent ion conductance through a direct action at the channel. The sodium channel and the channel for the nicotinic AChR have some similar properties (in both structure and sensitivity to drug action) and may have a common genetic origin. When an ACh molecule binds to the \( \alpha \) subunits of AChR, the AChR undergoes a 3-dimensional conformational change that opens the channel and results in increased sodium conductance, causing a local depolarization. The local depolarization spreads to an action potential or leads to muscle contraction when summed with the action of other receptors. Nicotinic receptors possess a relatively low affinity for ACh at rest. The affinity for ACh is increased during activation (through an allosteric mechanism which increases the likelihood of another molecule of acetylcholine binding to the other \( \alpha \) subunit). At high concentrations of ACh, the affinity for ACh becomes higher and the receptor subsequently becomes desensitized. The ionophore (ion channel) is open during the active state and local anesthetics may bind to the open channel.

**Physiology of Neuromuscular Transmission**

Motor nerve impulses (action potentials) traveling down from the motor neurons through the motor fibers of peripheral nerve terminals cause the skeletal muscle fibers at which they terminate to contract. The junction between the motor axon terminal and a muscle fiber (motor endplate) is called the neuromuscular or myoneural junction. The terminals of motor axons contain thousands of vesicles filled with ACh. When an action potential reaches the axon terminal, hundreds of these vesicles discharge their ACh onto a specialized area of postsynaptic membrane on the fiber. This area contains a cluster of transmembrane channels that are opened by ACh and let sodium ions diffuse in. The interior of a resting muscle fiber has a resting potential of about −95 mV. The influx of sodium ions reduces the charge, creating an end plate potential. If the end plate potential reaches the threshold voltage (approximately −50 mV), sodium ions flow in with a rush and an action potential is created in the fiber. The action potential sweeps down the length of the fiber just as it does in an axon. No visible change occurs in the muscle fiber during (and immediately following) the action potential. This period, called the latent period, lasts from 3-10 ms. Before the latent period is over, the enzyme acetylcholinesterase breaks down the ACh in the NMJ at a speed of 25,000 molecules per second, the sodium channels close, and the field is cleared for the arrival of another nerve impulse. The resting potential of the fiber is restored by an outflow of potassium ions. The brief (1-2 ms) period needed to restore the resting potential is called the refractory period.

**Presynaptic Steps Leading to Neurotransmitter Release**

The arrival of action potentials and invasion of nerve terminals causes depolarization. In many neurons only 10-20% of action potentials trigger transmitter re-