Diseases of the neuromuscular junction

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1 Introduction

The neuromuscular junction (NMJ) is a critical element in the intricate network of communication between the nervous and muscular systems. This junction serves as the interface where signals from the nervous system are translated into muscular contractions, allowing for the precise control and coordination of voluntary movements.

1.1 Definition of Neuromuscular Junction

The neuromuscular junction can be defined as the synapse or connection point between a motor neuron and a skeletal muscle fiber. It is a specialized structure that facilitates the transmission of nerve impulses from the motor neuron to the muscle fiber, ultimately leading to muscle contraction. The efficiency of this junction is paramount for the proper functioning of the muscular system and, consequently, for the execution of various voluntary movements.

1.2 Structural Components

The neuromuscular junction comprises several key structural components that contribute to its functionality. At the nerve terminal, synaptic end bulbs store and release neurotransmitters, specifically acetylcholine (ACh), into the synaptic cleft. The synaptic cleft, a narrow gap between the nerve terminal and the muscle fiber, separates the motor neuron and the muscle cell. On the muscle fiber side, specialized receptor sites, known as motor

end plates, are present. These receptor sites are highly sensitive to acetylcholine and play a pivotal role in transducing the chemical signal into a physiological response.

1.3 Mechanism of Action

The functioning of the neuromuscular junction is a highly orchestrated process that involves several sequential steps. The process begins with the propagation of an action potential along the motor neuron axon. This electrical impulse triggers the opening of voltage-gated calcium channels in the nerve terminal, leading to an influx of calcium ions. The increased calcium concentration within the nerve terminal prompts the fusion of synaptic vesicles containing acetylcholine with the cell membrane, facilitating the release of acetylcholine into the synaptic cleft.

Upon release, acetylcholine diffuses across the synaptic cleft and binds to the receptor sites on the motor end plate. This binding event induces a change in the permeability of the muscle cell membrane, leading to the generation of an action potential in the muscle fiber. The action potential then propagates along the muscle cell membrane and deep into the muscle fiber via the transverse tubules.

As the action potential reaches the sarcoplasmic reticulum, a specialized organelle in muscle cells, it triggers the release of calcium ions into the cytoplasm. The increased intracellular calcium concentration initiates the contraction of the muscle fiber by promoting the interaction between actin and myosin, the contractile proteins within muscle cells.

2 Myasthenia gravis

Myasthenia gravis (MG) is the most common disorder affecting the neuromuscular junction of the skeletal muscles. The classic presentation is a fluctuating weakness that is more prominent in the afternoon. It usually involves muscles of the eyes, throat (difficulty in swallowing), and extremities. The reduced transmission of electrical impulses across the neuromuscular junction due to the formation of autoantibodies against the specific postsynaptic membrane proteins consequently causes muscle weakness. A wide variety of conditions can precipitate MG, such as infections, immunization, surgeries, and drugs.

Myasthenia gravis causes a significant number of complications. These include myasthenic crisis, an acute respiratory paralysis that requires intensive care.

2.1 Etiology and pathophysiology

Myasthenia gravis is an autoimmune disorder where the body makes antibodies against either the acetylcholine receptor (AchR), that is, there are autoantibodies against the muscle acetylcholine nicotinic receptor. Myasthenia gravis is the most common disorder of neuromuscular transmission, which is characterized by fatigable muscle weakness, as mentioned. Approximately 10% of patients with MG have a thymoma, and it is implicated in the production of autoantibodies.

Autoantibodies bind to the ACh receptor present in the postsynaptic membrane of the skeletal muscles and activate the complement system leading to the formation of the membrane attack complex (MAC). MAC brings about the final degradation of the receptors. They act by functionally blocking the binding of ACh to its receptor or by enhancing the destruction of the ACh receptor.

2.2 History and Physical Examination

The main clinical feature of MG is the fluctuating muscle weakness that varies in severity, worsens with physical activity, and improves with rest. It can be precipitated by a wide

variety of factors like infections, surgery, immunization, heat, emotional stress, pregnancy, drugs, and worsening of chronic medical illnesses.

In history taking, patients should be asked about the timing of the symptoms, at what time of the day do the symptoms usually occurs, as well as improvement with rest. Inquire about subtle signs like coughing after swallowing, increase time to finish eating, hoarseness of the voice, easy fatiguability in the climbing up stairs, and slow and frequent errors in writing or typing; these symptoms are most prominent at the end of the day or work shift.

The most common symptoms include the following:

Extraocular Muscle Weakness: Around 85% of patients will have this on the initial presentation. Common patient complaints include diplopia, ptosis, or both. These symptoms can progress and cause generalized MG.

Bulbar Muscle Weakness: This can be the initial presentation in 15% of patients and causes symptoms like difficulty chewing or frequent choking, dysphagia, hoarseness, and dysarthria. The involvement of facial muscles causes an expressionless face, and neck muscle involvement causes a dropped-head syndrome.

Limb Weakness: This usually involves the proximal muscles more than distal muscles, with the upper limbs more affected than the lower limbs. Myasthenic crisis: It is due to the involvement of intercostal muscles and diaphragm and is a medical emergency.

There are no autonomic symptoms like palpitations, bowel, or bladder disturbances. The physical examination may reveal normal muscle power because of the fluctuating disease pattern. In such cases, repeated or sustained muscle contractions can demonstrate weakness. Improvement is seen after a period of rest. Based on the clinical features and the disease severity, myasthenia gravis can be divided into 5 main classes:

Class I: Involves any ocular muscle weakness.

Class II: Involves mild weakness of muscles other than ocular muscles: weakness of the limb, axial muscles, oropharyngeal, or respiratory muscles.

Class III: Involves muscles other than ocular muscles moderately.

Class IV: Involves severe weakness of affected muscles.

Class V: Involves intubation with mechanical ventilation.

2.3 Diagnosis

The diagnosis of myasthenia gravis is mostly clinical. The laboratory investigations and procedures usually aid the clinician in confirming the clinical findings.

Serologic Tests: The anti-AChR antibodies test is very specific, and it confirms the diagnosis in patients with classical clinical findings.

Electrophysiologic Tests: These tests assess for conduction delays in the NMJ. Routine nerve conduction studies are usually performed to determine the functioning of the nerves and muscles before undertaking these tests. Also, repeated nerve stimulation depletes the ACh in the NMJ, and produces a low excitatory postsynaptic potential (EPSP).

Edrophonium (Tensilon) Test: Edrophonium is a short-acting acetylcholinesterase inhibitor that increases the availability of ACh in the NMJ. This is particularly useful for ocular MG, where electrophysiologic testing cannot be performed. It is administered intravenously, and the patient is observed for improvement in the symptoms of ptosis or diplopia. It has a sensitivity of 71% to 95% for MG diagnosis.

2.4 Treatment and Management

The mainstay of treatment in MG involves cholinesterase enzyme inhibitors and immunosuppressive agents. Symptoms that are resistant to primary treatment modalities or those requiring rapid resolution of symptoms (myasthenic crisis), plasmapheresis or intravenous immunoglobulins can be used.

Symptomatic Treatment: Acetylcholinesterase inhibitors increases the level of ACh at the NMJ by preventing its enzymatic degradation. Pyridostigmine is the preferred one.

Immunosuppressive Treatment: These are indicated in patients who remain symptomatic even after pyridostigmine treatment. Glucocorticoids (prednisone, prednisolone, and methylprednisolone) or even azathioprine are the first-line immunosuppressive agents used in the treatment of MG.

Intravenous immunoglobulins and Plasmapheresis: These are recommended during the perioperative period to stabilize a patient before a procedure. It is also the treatment of choice for the myasthenic crisis due to its rapid onset of action and used in cases that are resistant to immunosuppressive drugs.

3 Lambert-Eaton Myasthenic Syndrome

Lambert-Eaton myasthenic syndrome (LEMS) is a neuromuscular junction disorder that may present as a paraneoplastic syndrome. The majority of cases are associated with small-cell lung cancer (SCLC). The primary clinical symptom is muscle weakness. The underlying pathophysiology involves the development of antibodies that target voltage-gated calcium channels (VGCCs) on presynaptic nerve terminals, resulting in reduced acetylcholine (ACh) neurotransmitter release.

LEMS is usually categorized as paraneoplastic. Approximately 60% of LEMS patients have an underlying tumor, with the paraneoplastic form predominantly associated with SCLC. LEMS is also associated with other malignancies, such as non-SCLC, lung carcinoma, prostate cancer, thymoma, and lymphoproliferative disorders. Research has shown that the diagnosis of LEMS can precede the diagnosis of SCLC by 5 to 6 years.

When clinical suspicion arises regarding LEMS, electromyography testing provides valuable assistance in confirming the diagnosis. Repetitive nerve stimulation (RNS) is an essential component.

Due to the strong association with malignancy, a diagnosis of LEMS warrants an immediate and extensive investigation for an underlying malignancy. The initial recommended imaging study is a computed tomography (CT) or magnetic resonance imaging (MRI) chest scan.

4 Botulism

Botulism is a neuroparalytic syndrome. It is a potentially fatal syndrome of diffuse, flaccid paralysis caused by botulinum neurotoxin (BoNT), an exo neurotoxin elaborated by the bacterium *Clostridium botulinum*.

Botulinum neurotoxin is considered the deadliest toxin known due to its high potency and lethality, with a lethal dose of 1 ng to 3 ng (nanograms) of toxin per kilogram (kg) of body mass. The flaccid paralysis of botulism is the result of irreversible inhibition of acetylcholine (ACh) release at the presynaptic nerve terminal of the body's neuromuscular

junctions (NMJs). Botulism can be acquired through exposure to the pre-formed toxin via improperly-stored food.

After exposure to BoNT, the time to symptom onset depends upon the dose of the toxin and the relevant kinetics of absorption. For food-borne botulism, symptoms typically appear within 12 to 72 hours of ingesting contaminated food. Treatment of botulism consists of antitoxin administration, hospital admission, close monitoring, respiratory support as required.