Diseases of the neuromuscular system
Common classes of neuromuscular disorders

• Myopathies
• Motor neuron disorders
• Peripheral nerve disorders
• Neuromuscular junction disorders
• Cerebellar disorders
MYOPATHY
Myopathies
The myopathies are neuromuscular disorders in which the primary symptom is muscle weakness due to dysfunction of muscle fiber. Other symptoms of myopathy can include muscle cramps, stiffness, and spasm. Myopathies can be inherited (such as the muscular dystrophies) or acquired.
Dystrophy
Genetic. Progressive weakness. Degeneration of skeletal muscles that control movement. Three most common types – Duchenne, facioscapulohumeral, myotonic. The three can be differentiated by the age of onset, the distribution of weakness, the rate of progression of the disease and the pattern of inheritance
Duchenne MD primarily affects boys and is the result of mutations in the gene that regulates dystrophin - a protein involved in maintaining the integrity of muscle fiber. Onset is between 3-5 years and progresses rapidly. Most boys become unable to walk at 12, and by 20 have to use a respirator to breathe.

Facioscapulohumeral MD appears in adolescence and causes progressive weakness in facial muscles and certain muscles in the arms and legs. It progresses slowly and can vary in symptoms from mild to disabling.

Myotonic MD varies in the age of onset and is characterized by myotonia (prolonged muscle spasm) in the fingers and facial muscles; a floppy-footed, high-stepping gait; cataracts; cardiac abnormalities; and endocrine disturbances. Individuals with myotonic MD have long faces and drooping eyelids; men have frontal baldness (have trouble releasing a grip – grip test)
Distribution of weakness

Duchenne
Generalized weakness and muscle wasting affecting the limbs and trunk muscles first. Calves often enlarged.

Facioscapulohumeral (Landouzy-Dejerine)
Facial muscle weakness with weakness and wasting of shoulders and upper arms.

Myotonic (Steinert’s disease)
Generalized weakness, muscle wasting affecting face, feet, hands and neck first. Delayed relaxation of muscle.
Age of onset

Duchenne
Age 2-6 yrs

Facioscapulohumeral Dystrophy (Landouzy-Dejerine)
Childhood to early adulthood

Myotonic (Steinert’s disease)
Childhood to middle age
Rate of progression

Duchenne
Disease progresses slowly but will affect all voluntary muscles. Survival is rare beyond 20.

Facioscapulohumeral dystrophy (Landouzy-Dejerine)
Progresses slowly with some periods of rapid deterioration

Myotonic dystrophy (Steinert’s disease)
Progress is slow sometimes spanning 50 to 60 years
Pattern of inheritance

Duchenne
X-linked recessive (females are carriers)

Facioscapulohumeral Dystrophy (Landouzy-Dejerine)
Autosomal dominant

Myotonic dystrophy (Steinert)
Autosomal dominant
Human genome consists of 23 pairs of chromosomes. Twenty two of these pairs are not related to gender and are called autosomal chromosomes. The 23rd pair is called sex chromosomes.
Genetic sequence which dictates the proteins which are produced in our body is called genes. Changes in our genes can cause faulty proteins to be produced in the body. The genetic changes are called mutations. Not all mutations are bad.
Genes can be dominant or recessive.

Dominant – Only one of the gene has to be present to be expressed
Recessive - A pair of the genes have to be present to be expressed

If an individual only has one of a recessive gene – that person is a carrier
Autosomal inheritance – genes responsible are on the autosomal chromosomes
X linked inheritance – they are found on the sex chromosomes (X)
Autosomal transmission

Autosomal dominant – Trait is carried by a gene on the autosomes. Only one parent has to have the disease

Autosomal recessive – Trait is carried by a gene on the autosomes. Both parents can be carriers.
Autosomal dominant

Mother or father can be affected. Boys and girls have equal risk for the disease.
Autosomal recessive

Mother or father can be carriers. Boys and girls have equal risk for the disease
Sex linked transmission

X-linked recessive – Only one parent has to transmit the mutant gene. These X linked diseases usually occur in boys. Even though the Y chromosome is the matching chromosome to the X, it lacks many of the chromosomes which are present on the X chromosome. For this reason a defect on the X chromosome is quickly manifested. For this reason too, the mother is usually the carrier of the disease.
Sex linked transmission

X linked dominant – extremely rare. Both boys and girls have an equal possibility of inheriting these diseases.
X linked recessive

Mother is usually the carrier. Boys are at a higher risk.
X-linked recessive

In many cases, even though the son has a recessive gene on the X chromosome, there is no matching gene on the Y chromosome to correct the defect – so the son will manifest the genetic problem.
Knockout mice

Provide in vitro and in vivo models of mutant genes in humans
The cellular basis of Duschenne

• Primarily affects boys (1/3500 boys)

• Recessive sex linked trait – found on X chromosome

• Mutant gene sequence has been cloned

• The mutant gene codes for the protein dystrophin

• Dystrophin is a protein that helps to anchor the cytoskeleton of muscular cells to the extracellular matrix. It enables the cell to withstand the stress of muscle contraction. In people with this disease, the expression of the protein is either absent or limited.
The cellular basis of Duschenne

• Currently the presence of the mutant allele can be detected in pregnant women.

• Some current research is concentrating on gene therapy to restore the expression of dystrophin
Genetic studies reveal that the mutation creating DMD is found on a segment of the X chromosome responsible for producing the protein dystrophin. Dystrophin plays an important role in anchoring the muscle cell to the extracellular matrix, thus enabling the cell to withstand the stress of contraction.
Myotonic MD – Defective protein kinase

One of the myotonic dystrophy genes is found on chromosome 19. It is caused by a repeat disorder of the genes.
Myotonic MD – Defective protein kinase

The mutant gene is inherited in an autosomal dominant pattern. Inheriting the mutant gene from one parent will create problems. There is a 50% chance of inheriting the disease from an affected parent. It codes for a protein kinase that is found in skeletal muscles. Protein kinases are enzymes that are necessary for alterations in proteins.
MOTOR NEURON DISORDERS
Motorneuron disorders

Motorneurons are cells in the nervous system which send signals concerning movement. These neurons can be divided into upper and lower motorneurons.

- Upper motorneurons – start in motor cortex and terminate in the medulla of the brain or in the spinal cord.
Motorneuron disorders

Upper motoneurons synapse with the lower motorneurons.

- Lower motorneurons - These are the neurons which finally carry the message of the central nervous system to the muscles.
Motorneuron diseases are in fact quite rare 2 per 100,000. The age of onset is mid to late adult life. Life expectancy from the disease is 1-5 years but it can last longer. There have been some famous patients with this disorder.
Amyotrophic lateral sclerosis (ALS)
As motor neurons degenerate, they can no longer send impulses to the muscle fibers that normally result in muscle movement. Early symptoms of ALS often include increasing muscle weakness, especially involving the arms and legs, speech, swallowing or breathing.
When muscles no longer receive messages from the motor neurons that they require to function, the muscles begin to atrophy (become smaller). Limbs begin to look "thinner" as muscle tissue atrophies.
Features of upper motorneuron disorders

• muscle spasticity
• slowed recruitment of voluntary muscle strength
• weakness especially in extensors of upper limbs and flexors of lower limbs
• increased reflexes
• Pseudobulbar palsy
Features of lower motorneuron disorders

• muscle wasting
• muscle fasciculation
• reduced muscle tone
• weakness
• depressed reflexes
• bulbar palsy
Bulbar palsy

Bulbar - lower brainstem, which is the control center for the cranial nerves 7-12.

Palsy - weakness.

Symptoms would include trouble speaking, swallowing, coughing, using the tongue, and perhaps some trouble with facial expression.

Bulbar palsy – neurons in the brainstem are damaged.

Pseudobulbar palsy – no damage to brainstem, but damage to the cerebral cortex which sends signals to the brainstem.
The most common forms of motorneuron diseases are

- Amyotrophic lateral sclerosis (ALS)
- bulbar palsy
- progressive muscle atrophy
- primary lateral sclerosis
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Several theories concerning the reasons for ALS
Can be acquired or genetic
• It could be due to an oxidative stress
• It could be an autoimmune reaction of the body
Oxidative stress

Your body constantly reacts with oxygen as you breathe and your cells produce energy. As a consequence of this activity, highly reactive molecules are produced known as free radicals.

Free radicals interact with other molecules within cells. This can cause oxidative damage to proteins, membranes and genes.

Oxidative damage has been implicated in the cause of many diseases such as cancer and Alzheimer's and has an impact on the body's aging process.

External factors such as pollution, sunlight and smoking also trigger the production of free radicals.
Antioxidants

To counteract oxidative stress, the body produces antioxidants to defend itself. It's the job of antioxidants to neutralise or 'mop up' free radicals that can harm our cells.

Your body's ability to produce antioxidants (its metabolic process) is controlled by your genetic makeup and influenced by your exposure to environmental factors such as diet and smoking.

Changes in our lifestyles, which include more environmental pollution and less quality in our diets, mean that we are exposed to more free radicals than ever before.
It is due to an oxidative stress

In about 10% of patients with MND, a family history of the disease can be identified. Usually this shows a pattern of autosomal dominant inheritance. Genetic mutations in the gene, which codes for the enzyme superoxide dismutase or SOD 1 on chromosome 21 are present in about 20% of familial cases.

Superoxide dismutase is a detoxification enzyme which helps to control the damage in the body which may be caused by the presence of free radicals.
ALS is due to an autoimmune mechanism of the body

In this disease, the immune system becomes confused and begins attacking tissues in the body. Under normal conditions, the body's immune system produces proteins called immunoglobulins which attach to their target antigen. An antigen is a substance that produces an immune response and is usually something foreign to the body.
The immune system
Peripheral neuropathies
Peripheral neuropathies

The peripheral nervous system is the network that transmits information from the brain and spinal cord to the rest of the body. They also send sensory information back to the brain and spinal cord such as cold fingers or burns.
Neuropathies can be classified in many ways:

One method of classification is based on the number of nerves damaged

**Mononeuropathy** – damage to one nerve or nerve group, isolated problem. Caused by trauma or pressure on a nerve. The damage is often to the myelin sheath, thus slowing down nerve conduction. eg Carpal tunnel syndrome

**Polyneuropathy** – diffuse damage to the nerves. eg seen in diabetics, alcoholics.
Mononeuropathy- Carpal tunnel syndrome

Damage to the median nerve which passes through the carpal tunnel
Peripheral polyneuropathy - Diabetes

Generalized nerve damage affecting nerves to the arms and legs. Symptoms include

• numbness or insensitivity to pain
• tingling, burning or prickling
• sharp pains or cramps
• extreme sensitivity to light touch
• loss of balance and coordination
Peripheral neuropathies can also be classified based on the kind of nerves damaged – motor, sensory, autonomic

Motor nerve damage – muscle weakness. Painful cramps and fasciculations (muscle twitching visibly under the skin). Muscle loss.

Sensory nerve damage – sense of numbness. Feel as if you are wearing stockings and gloves. Loss of ability to recognize objects by touch. Neuropathic pains.
Peripheral neuropathies can also be classified based on the kind of nerves damaged – motor, sensory, autonomic.

Autonomic nerve damage – autonomic nerves regulate involuntary functions such as breathing, blood pressure, sexual function, digestion. So the damage to these nerves can cause diverse malfunctions.
Physiological causes

Primarily damage to the axon – Frequently to the myelin sheath and sometimes the degeneration of the axon itself. The damage is frequently distal. The axons degenerate in a fashion which is distal to proximal.
Causes of peripheral neuropathies

Inherited eg Charcot Marie tooth neuropathy

Acquired – trauma, systemic disease - metabolic or hormonal eg diabetes where 60-70% of the patients suffer from polyneuropathy
Charcot Marie tooth neuropathy

- One of the most common inherited neurological disorders 1/2500 people.

- Caused by mutation in gene producing protein for myelinization
Charcot Marie tooth neuropathy

• Typical features – weakness of foot and lower leg muscles which result in foot drop and high stepping gait with frequent tripping and falling. Foot deformities such as high arches and hammertoes. Lower legs may take on an inverted champagne bottle appearance.
Charcot Marie tooth neuropathy

- onset of symptoms – adolescence, early adulthood
- CMT disorder is not fatal – many people do not even know they have it.
Neuromuscular Junction
Problems of neuromuscular junction

a) Myasthenia gravis

b) Botulism
The neuromuscular junction

Neurotransmitter: Acetylcholine
Receptor: nAChR (nicotinic Acetylcholine Receptor)
Myasthenia gravis

- autoimmune disorder. Antibodies attack the ACh receptors on skeletal muscles. Thought to be a malfunction of the thymus gland. Abnormal levels of antibodies to the acetylcholine receptor are found in the blood.
Myasthenia gravis is caused by a problem at the junction between the nerve endings and the muscle fibres.

A nerve ending

Acetylcholine is released from nerve ending

Antibody

Surface of muscle fibre

Some receptors are stimulated by acetylcholine

Neuromuscular junction (gap between nerve and muscle)

Receptor on surface of muscle fibre

Some receptors are blocked or damaged by antibodies
Myasthenia gravis

• more common among women

• The first symptoms are usually drooping eyelids and weak eye muscles that cause double vision.

• Other symptoms develop later – difficulty speaking, swallowing; local fatigue of muscles after repetitive use. The fatigue is not general but isolated to particular muscle groups.
Myasthenia gravis

- Drugs utilized are the following:
  
  i) drugs that increase acetylcholine
  
  ii) drugs that suppress the body immune reactions
  
  iii) drugs that decrease the activity of acetylcholinesterase
Botulism

Poisoning from toxins produced by the bacteria Clostridium botulinum. These toxins paralyze the muscles by inhibiting the release of acetylcholine.

Symptoms

Drooping eyelids, double vision, difficulty speaking, swallowing. Muscles become weaker but muscle sensation remains.
Botulism

The toxin is frequently in jars or cans of food. If spores are present, they grow and reproduce in conditions of moisture, nutrition and low O2.

BUT Even if the spores are resistant to heat, the toxins are destroyed by heating food near 100 degrees centigrade for 30 mins.
Cerebellar disorders
Cerebellum
Cerebellar disorders

• Ataxia – defective posture maintenance, lack of coordination, tremor and the inability to produce small movements – this is most pronounced during the termination of the movement.

• Other consequences of cerebellar disorders – slurred speech (dysarthria) and nystagmus (abnormal eye movements)

• hereditary, acquired (toxins, trauma, tumours)
Hereditary ataxia

• Episodic ataxia 1 and 2

• Examples of channelopathies

  EA 1 – due to mutation producing defective K+ channel

  EA2 – due to mutation producing defective Ca2+ channel

• Other examples of channelopathies – cystic fibrosis, migraine, myotonia (muscles are able to contract but not relax), several forms of epilepsies
Excitable cells – cardiac, muscular, nervous

Differential ion distribution across the cell membrane
Ionic channels - Gates to the passage of these ions

Passage of ions is determined by variables such as size of pore and charge
Ionic channels are large protein macromolecules.
Neurotransmitters or voltage
Common classes of neuromuscular disorders

- Myopathies
- Motor neuron disorders
- Peripheral nerve disorders
- Neuromuscular junction disorders
- Cerebellar disorders
Use of physical therapy

There is no cure in the case of many of these illnesses. Physical therapy is therefore essential in improving synaptic connections and increasing muscular strength.