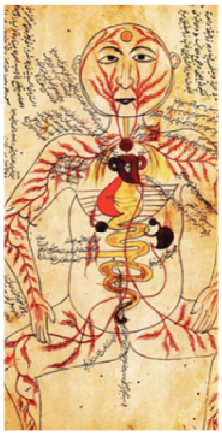

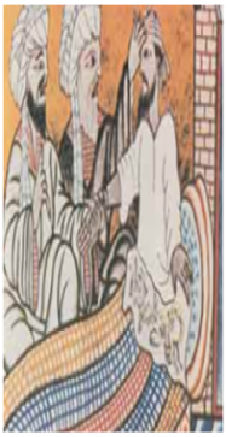

NEUROLOGY

For undergraduate

Prepared by

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2014

Contributors

CONTENTS

Introduction &Anatomy

(Dr.Hosna Saad)

- Neurology deals with the diagnosis and treatment of all categories of disease involving the central and peripheral nervous system; or equivalently, the autonomic nervous system and the somatic nervous system, including their coverings, blood vessels, and all effector tissue, such as muscle.
-
- The nervous system is responsible for coordinating all of the body's activities. It controls not only the maintenance of normal functions but also the body's ability to cope with emergency situations.

Anatomy of the nervous system

The nervous system is divided into two parts:

1. **The central nervous system**: consisting of the brain and spinal cord. These structures are protected by bone and cushioned from injury by the cerebrospinal fluid (CSF)
2. **The peripheral system**: which connects the central nervous system to the rest of the body. The autonomic nervous system (divided into the sympathetic and parasympathetic nervous system) is also considered to be a part of the PNS and it controls the body's many vegetative (non-voluntary) functions.

❖ The Central Nervous system

I) Brain:

The brain is composed of the cerebrum, cerebellum, and brainstem.

a) The **cerebrum** is the largest part of the brain and is composed of right and left hemispheres. It performs higher

functions like interpreting touch, vision and hearing, as well as speech, reasoning, emotions, learning, and fine control of movement.

- The cerebral hemispheres have distinct fissures, which divide the brain into lobes. Each hemisphere has 4 lobes: frontal, temporal, parietal, and occipital.

b) The **cerebellum** is located under the cerebrum. Its function is to coordinate muscle movements, maintain posture, and balance.

c) The **brainstem** includes the midbrain, pons, and medulla. It acts as a relay center connecting the cerebrum and cerebellum to the spinal cord.

- It performs many automatic functions such as breathing, heart rate, body temperature, wake and sleep cycles, digestion, sneezing, coughing, vomiting, and swallowing.
- Ten of the twelve cranial nerves originate in the brainstem.

❖ The surface of the cerebrum has a folded appearance called the cortex.
❖ The cortex contains about 70% of the 100 billion nerve cells.
❖ The nerve cell bodies forming the cortex named gray matter and its axons make up the white matter.
❖ Each fold is called a **gyrus**, and each groove between folds is called a **sulcus**.

- Messages within the brain are carried along pathways.
- Messages can travel from one gyrus to another, from one lobe to another, from one side of the brain to the other, and to structures found deep in the brain (e.g. thalamus, hypothalamus).

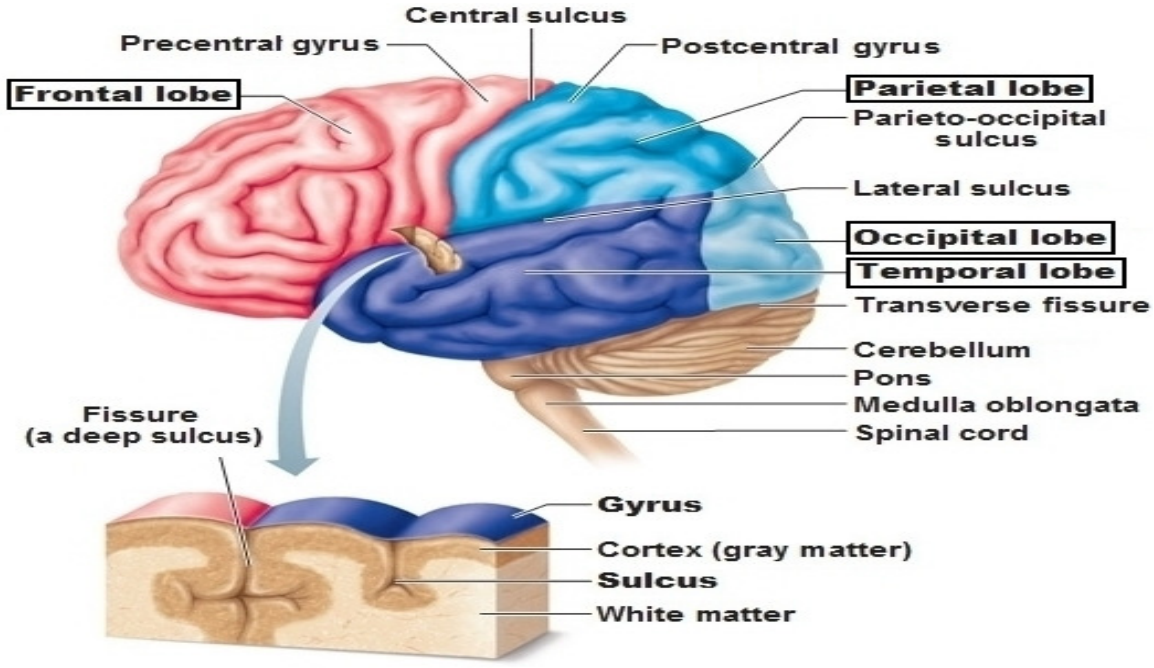
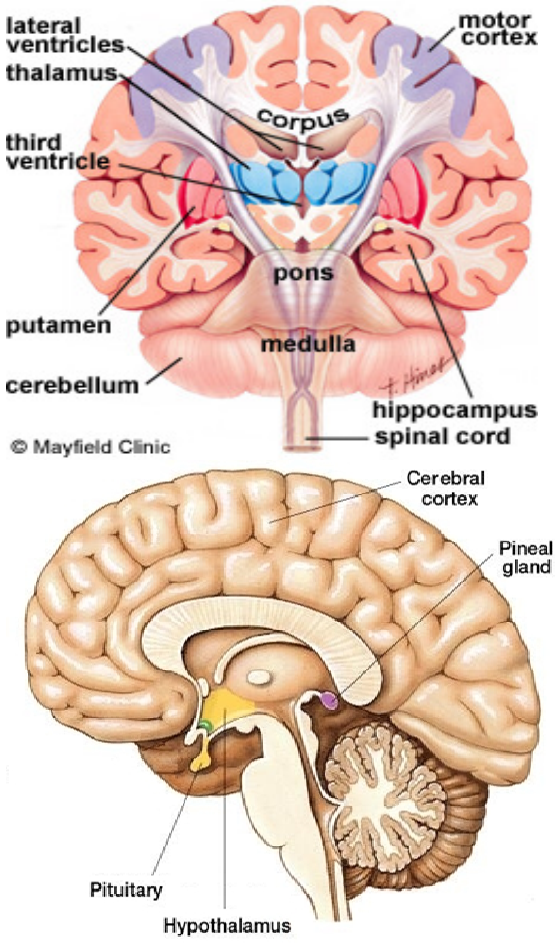


Figure 3. The brain is composed of three parts: the brainstem, cerebellum, and cerebrum.
The cerebrum is divided into four lobes: frontal, parietal, temporal, and occipital.

❖ ***Deep structures***

a) **Hypothalamus -** is located in the floor of the third ventricle and is the master control of the autonomic system. It plays a role in controlling behaviors such as hunger, thirst, sleep, and sexual response. It also regulates body temperature, blood pressure, emotions, and secretion of hormones.
b) **Pituitary gland** - lies in a small pocket of bone at the skull base called the sella turcica. The pituitary gland is connected to the hypothalamus of the brain by the pituitary stalk. Known as the "master gland," it controls other endocrine glands in the body.
c) **Pineal gland** - is located behind the third ventricle. It helps regulate the body's internal clock and circadian rhythms by secreting melatonin. It has some role in sexual development.
d) **Thalamus** - serves as a relay station for almost all information that comes and goes to the cortex. It plays a role in pain sensation, attention, alertness and memory.
e) **Basal ganglia** - includes the caudate, putamen and globus pallidus. These nuclei work with the cerebellum to coordinate fine motions, such as fingertip movements.

f) **Limbic system** - is the center of our emotions, learning, and memory. Included in this system are the cingulate gyri, hypothalamus, amygdala (emotional reactions) and hippocampus (memory).



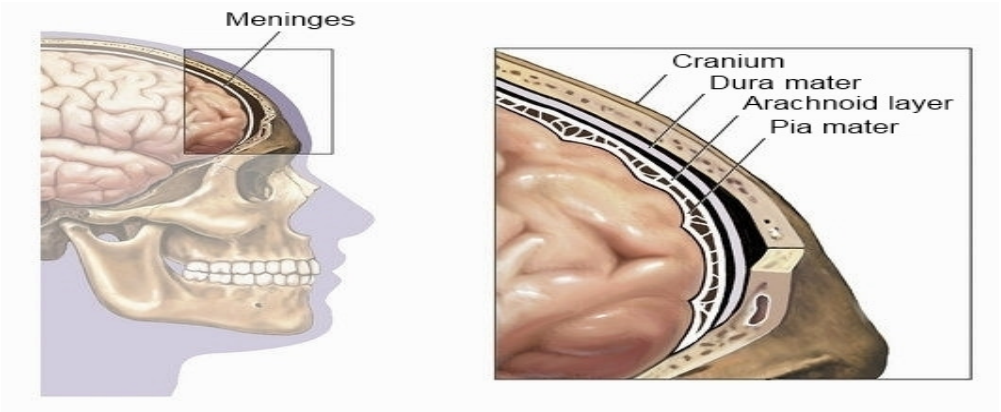
❖ ***Meninges***

The brain and spinal cord are covered and protected by three layers of tissue called meninges. From the outermost layer inward they are: the dura mater, arachnoid mater, and pia mater.

a) The **dura mater** is a strong, thick membrane that closely lines the inside of the skull; its two layers, the periosteal and meningeal dura, are fused and separate only to form venous sinuses. The dura creates little folds or compartments. There are two special dural folds, the falx and the tentorium. The falx separates the right and left hemispheres of the brain and the tentorium separates the cerebrum from the cerebellum.

b) The **arachnoid mater** is a thin, web-like membrane that covers the entire brain. The arachnoid is made of elastic tissue. The space between the dura and arachnoid membranes is called the subdural space.

c) The **pia mater** hugs the surface of the brain following its folds and grooves. The pia mater has many blood vessels that reach deep into the brain. The space between the arachnoid and pia is called the subarachnoid space. It is here where the cerebrospinal fluid bathes and cushions the brain.



❖ ***Ventricles and cerebrospinal fluid***

- The brain has hollow fluid-filled cavities called ventricles.
- Inside the ventricles is a ribbon-like structure called the choroid plexus that makes clear colorless cerebrospinal fluid (CSF).
- CSF flows within and around the brain and spinal cord to help cushion it from injury.
- This circulating fluid is constantly being absorbed and replenished.
- There are two ventricles deep within the cerebral hemispheres called the ***lateral ventricles***.
- They both connect with the ***third ventricle*** through a separate opening called the **foramen of Monro**.
- The third ventricle connects with the ***fourth ventricle*** through a long narrow tube called the **aqueduct of Sylvius**.
- From the fourth ventricle, CSF flows into the **subarachnoid space** where it bathes and cushions the brain.
- CSF is recycled (or absorbed) by special structures in the superior sagittal sinus called **arachnoid villi**.

- A balance is maintained between the amount of CSF that is absorbed and the amount that is produced. A disruption or blockage in the system can cause a build up of CSF, which can cause enlargement of the ventricles (hydrocephalus) or cause a collection of fluid in the spinal cord (syringomyelia).

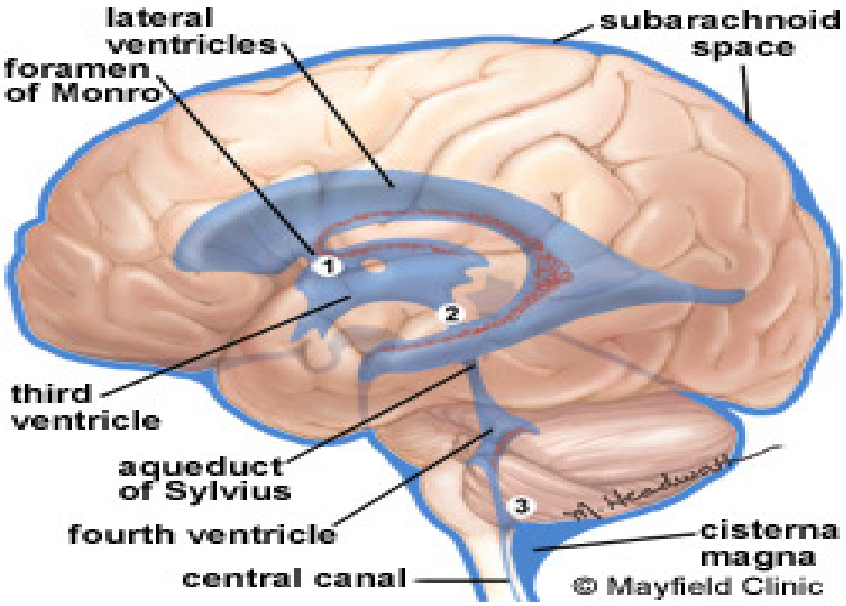


Figure 7. CSF is produced inside the ventricles deep within the brain. CSF fluid circulates inside the brain and spinal cord and then outside to the subarachnoid space. Common sites of obstruction: 1) foramen of Monro, 2) aqueduct of Sylvius, and 3) obex.

❖ ***Blood supply***

- **Arterial Circulation:**

- Blood is carried to the brain by two paired arteries, the internal carotid arteries (anterior cerebral circulation) and the vertebral arteries (posterior cerebral circulation).
- The internal carotid arteries supply most of the cerebrum.
- The vertebral arteries supply the cerebellum, brainstem, and the underside of the cerebrum.
- Both "communicate" with each other at the base of the brain called the Circle of Willis.

- ✓ **Anterior cerebral circulation**

The **anterior cerebral circulation** is the blood supply to the anterior portion of the brain. It is supplied by the following arteries:

1. **Internal carotid arteries**: These large arteries are the left and right branches of the common carotid arteries in the neck which enter the skull, as opposed to the external carotid branches which supply the facial tissues. The internal carotid artery branches into the anterior cerebral artery and continues to form the middle cerebral artery. It also give the ophthalmic artery and anterior choroidal artery.
2. **Anterior cerebral artery (ACA)**: which has ***cortica***l branch (supplying medial surface of the frontal lobe including prefrontal cortex, paracentral lobule and medial surface of motor area for lower limb) and ***capsular*** branch (Heubners artery, supplying the ventral half of the anaterior limb of internal capsule)
    a. Anterior communicating artery: Connects both anterior cerebral arteries, within and along the floor of the cerebral vault.
3. **Middle cerebral artery (MCA)**: which has ***cortica***l branches (supplying lateral surface of the frontal lobe and parietal lobe and anterior part of temporal lobe) and ***capsular*** branch (lenticulostriate artery, supplying the dors hallf of internal capsule)

- ✓ **Posterior cerebral circulation**

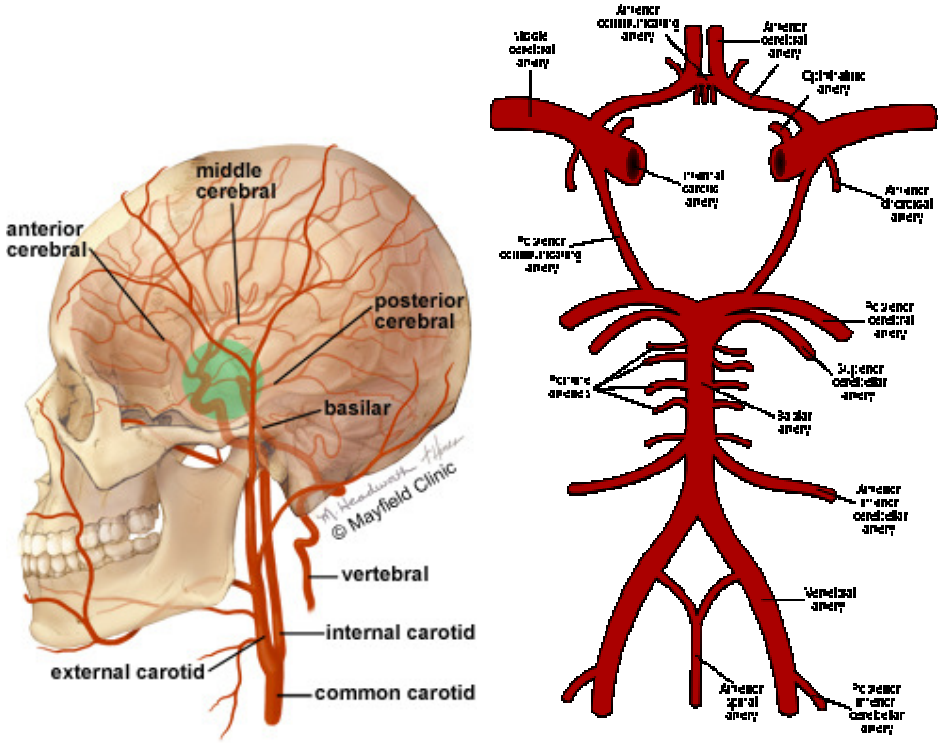
The **posterior cerebral circulation** is the blood supply to the posterior portion of the brain, including the occipital lobes, cerebellum and brainstem. It is supplied by the following arteries:

1. **Vertebral arteries**: These smaller arteries branch from the subclavian arteries. Within the cranium the two vertebral arteries fuse into the basilar artery.
    a. Posterior inferior cerebellar artery (PICA)
    b. Two spinal arteries which unit forming one anterior spinal artery.
2. **Basilar artery**: Supplies the midbrain, cerebellum, and usually branches into the posterior cerebral artery
    a. Anterior inferior cerebellar artery (AICA)
    b. Pontine branches

c. Superior cerebellar artery (SCA)

3. **Posterior cerebral artery (PCA)**: which has cortical branch (supplying posterior part of the temporal lobe and whole occipital) and capsular branch (***Thalamogeniculate*** artery, supplying the ventral half of the posterior limb of internal capsule)

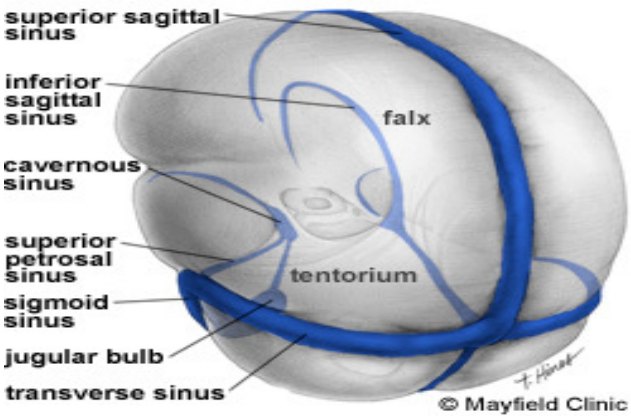
4. **Posterior communicating artery**



Venous Circulation:

- The venous circulation of the brain is very different than the rest of the body.
- The major vein collectors are integrated into the dura to form venous sinuses.
- The venous sinuses collect the blood from the brain and pass it to the internal jugular veins.
- The superior and inferior sagittal sinuses drain the cerebrum, the cavernous sinuses drains the anterior skull base.
- All sinuses eventually drain to the sigmoid sinuses, which exit the skull and form the jugular veins.

- These two jugular veins are essentially the only drainage of the brain.



II) ***Spinal Cord:***

❖ ***General Structure***:

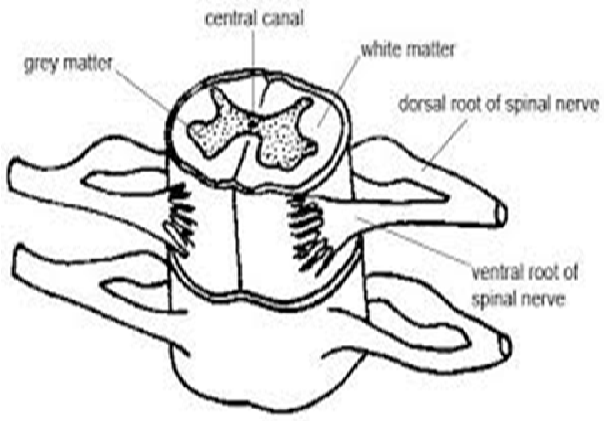
- The spinal cord is about 45 cms long, extending from the medulla down to the second lumbar vertebrae. It acts as a message pathway between the brain and the rest of the body.
- It is formed of grey matter resembling the letter (H: 2 anterior and 2 posterior horns) surrounded by white matter (ascending & desending tracts).
- Formed of 31 segments: 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, 1 coccyx, ends at L1 and continue as Cauda equina (collection of lumbosacral roots).
- Conus Medullaris: S3, 4,5
- Eiconus: l4, 5, S1, 2

❖ ***Blood supply***:

Three arteries provide blood supply to the spinal cord by running along its length. These are the two **Posterior Spinal Arteries** and the one **Anterior Spinal Artery**. These travel in the subarachnoid space and send branches into the spinal cord that communicate with branches from arteries on the other side.

❖ ***Function:***

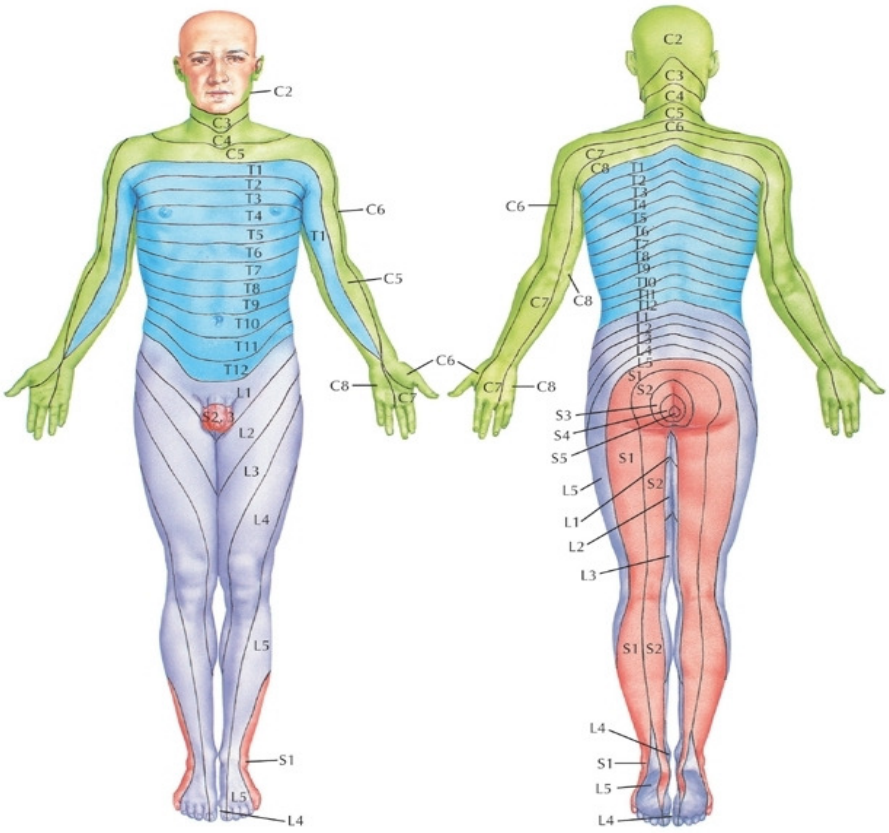
The spinal cord is divided into 33 different segments. At every segment, pair of spinal nerves (right and left) exit the spinal cord and carry motor (movement) and sensory information.



These nerves combine to supply strength to various muscles throughout the body as follows:

C1-C6: Neck flexion
C1-T1: Neck extension
C3-C5: Diaphragm
C5-C6: Shoulder movement and elbow flexion
C6-C8: Elbow and wrist extension
C7-T1: Wrist flexion
C8-T1: Hand movement
T1-T6: Trunk muscles above the waiste
T7-L1: Abdominal muscles
L1-L4: Hip flexion
L2-L4: Thigh adduction
L4-S1: Thigh abduction
L2-L4: Knee extension
L5-S2: Hip extension
L4-S2: Knee flexion
L4-S1: Foot dorsiflexion (move upward) and toe extension
L5-S2: Foot plantar flexion (move downward) and toe flexion

The spinal nerves also provide sensation to the skin in an organized manner as depicted below.



Tracts:

Ascending Tracts:	***Descending tracts***
▪ Dorsal spinocerebral tract ▪ Ventral spinocerebellar tract ▪ Spinocervical thalamic tract ▪ Lateral spionothalamic tract ▪ Anterior spinothalamic tract	▪ Corticospinal tract ▪ Rubrospinal tract ▪ Lateral vestibulospinal tract ▪ Medial vestibularspinal tract ▪ Reticulospinal tract ▪ Descending autonomic pathway

❖ Peripheral Nervous System:

- The peripheral system connects the central nervous system to the rest of the body. The main divisions of the Peripheral Nervous System are:

  a) The autonomic nervous system — which controls the automatic functions of the body: the heart, smooth muscle (organs) and glands. It is divided into the "fight-or-flight" system and the "resting and digesting" system.
  b) The somatic nervous system — which allows us to consciously or voluntarily control our skeletal muscles.

  - The somatic system contains 12 cranial nerves and 31 spinal nerves.

❖ Cranial nerves:

- The brain communicates with the body through the spinal cord and twelve pairs of cranial nerves.
- Ten of the twelve pairs of cranial nerves that control hearing, eye movement, facial sensations, taste, swallowing and movement of the face, neck, shoulder and tongue muscles originate in the brainstem.
- The cranial nerves for smell and vision originate in the cerebrum.

Function	**Name**	**Number**
Smell	Olfactory	I
Sight	Optic	II
moves eye, pupil	oculomotor	III
moves eye	trochlear	IV
face sensation	trigeminal	V
moves eye	abducens	VI
moves face, salivate	Facial	VII
hearing, balance	vestibulocochlear	VIII
taste, swallow	glossopharyngeal	IX
heart rate, digestion	Vagus	X
moves head	accessory	XI

moves tongue	hypoglossal	XII

❖ Functional anatomy:

The brain is made up of two types of cells: nerve cells (neurons) and glia cells.

a) **Nerve cells**

- Neurons are comprised of a dendrite, a cell body and an axon.
- Impulses travel to the dendrite into the cell body and then onto the axon. A special sheath called myelin, which increases the conductivity of the neuron, covers some nerves.
- As messages travel from one neuron to the next they move across a synapse.
- At each synapse there is a chemical called a neurotransmitter. At various parts of the body specific neurotransmitters facilitate communication, for example dopamine (motor function), serotonin (mood) and endorphins (painkillers).
- Sensory neurons carry messages from a receptor to the brain. The brain then interprets the message.
- Motor neurons then send the message to an affector in muscles and glands.

b) **Glia cells**

- Glia are the cells of the brain that provide neurons with nourishment, protection, and structural support. There are about 10 to 50 times more glia than nerve cells and are the most common type of cells involved in brain tumors.

    - Astroglia or astrocytes transport nutrients to neurons, hold neurons in place, digest parts of dead neurons, and regulate the blood brain barrier.

    - Oligodendroglia cells provide insulation (myelin) to neurons.

    - Ependymal cells line the ventricles and secrete cerebrospinal fluid (CSF).

- Microglia digest dead neurons and pathogens.

• Physiology of the nervous system:

The nervous system has three general functions: a sensory function, an interpretative function and a motor function.

1. Sensory nerves gather information from inside the body and the outside environment. The nerves then carry the information to central nervous system (CNS).
2. Sensory information brought to the CNS is processed and interpreted.
3. Motor nerves convey information from the CNS to the muscles and the glands of the body.

1) Sensory function (Sensory system):

- A **sensory system** is a part of the nervous system responsible for processing sensory information. A sensory system consists of sensory receptors, neural pathways, and parts of the brain involved in sensory perception.
- **Types of sensation:**

1- somatic sensations: include

- Superficail sensation: pain, temperature and touch
- Deep sensation: vibration, joint, muscle and nerve sense.
- Cortical sensations: tactile localization, two point descrimination, perceptual rivalery, stereognosis, and graphosthesia.

2- Visceral sensation: all sensation from internal viscera.
3- Special sensation: vision, hearing, smell and taste.

• Somatic sensory system:

A somatosensory pathway will typically have three long neurons: primary, secondary and tertiary (or first, second, and third).

- The *first* neuron always has its cell body in the dorsal root ganglion of the spinal nerve (if sensation is in parts of the head or neck not covered by the cervical nerves, it will be the trigeminal nerve ganglia or the ganglia of other sensory cranial nerves).
- The *second* neuron has its cell body either in the spinal cord or in the brainstem. This neuron's ascending axons will cross (decussate) to the opposite side either in the spinal cord or in the brainstem. The axons of many of these neurons terminate in the thalamus (for example the ventral posterior nucleus, VPN), others terminate in the reticular system or the cerebellum.
- In the case of touch and certain types of pain, the *third* neuron has its cell body in the VPN of the thalamus and ends in the postcentral gyrus of the parietal lobe.
- Somatic Sensations has two pathways: posterior column (for deep sensation and fine touch) and anterolateral system (for superficial sensation)

Spinal: Anterolateral system (ALS)	*Spinal: Dorsal column-medial lemniscal system*	
Temperature (warm, cold), pain, itch, crude touch	Fine touch, pressure, vibration, proprioception	Modalities
A-delta & C-fiber	A-beta	1st order axon
Dorsal root ganglion	Dorsal root ganglion	1st order cell body
Synapse shortly after entering spinal cord or may ascend few segments forming lissauer tract	Dorsal columns	1st order path in C.N.S.
Spinal dorsal horn: - Substantia gelatinosa of rolandi (SGR): for pain and temperature - Main sensory nucleus: for crude touch	Medulla, cuneate (from upper body) and gracillis (from lower body) nuclei	2nd order cell body
Cross in spinal cord, ascend in spinoreticular and anterolateral tracts - Lateral spinothalamic: for pain and temperature - Ventral spinothalamic	Cross in medulla, ascend in medial lemniscus	2nd order axon

tract for crude touch.		
Thalamus VPL (spinothalamic) and intralaminar nuclei (spinoreticular)	Thalamus VPL nucleus	3rd order cell body

EFFECTS OF PERIPHERAL AND SPINAL CORD LESIONS

Motor effect of lesion (skeletal muscle)	*Sensory effect of Lesion*	*Site of Lesion*
Flaccid paralysis of muscles innervated by nerve (LMN lesion); no reflex, muscle atrophy, fasciculations	Anesthesia of peripheral nerves receptive field	Peripheral nerve
Impaired coordination due to reduced proprioceptive feedback	Anesthesia of corresponding dermatomes	Dorsal root or dorsal root ganglion
Flaccid paralysis or paresis	No effect	Ventral root or alpha-motoneuron
Spastic paralysis below the level of the section (UMN lesion); enhanced reflex & tone, clonus, Babinski sign	Anesthesia below the level of the section	Total section of the spinal cord
Below the level of the section, ipsilateral paresis or spastic paralysis	Below the level of the section, loss of ipsilateral touch-pressure and contralateral pain-temperature	Hemisection of the spinal cord (right or left side); note effect of selective lesion in the dorsal quadrant only (sensory effects) or ventral quadrant only (motor effects)
Contralateral hemiplegia	Contralateral hemihyposthesia	somatosensory cortex

II) Interpretative function (The Cerebral Lobes and cortical areas):

- Each cerebral hemisphere is divided into four lobes; the **frontal**, **parietal**, **temporal**, and the **occipital**.

I) The **Frontal Lobe** is the most anterior lobe of the brain. Its posterior boundary is the fissure of Rolando, or **central sulcus**, which separates it from the parietal lobe. Inferiorly, it is divided from the temporal lobe by the **fissure of Sylvius** which is also called the **lateral fissure**.

1- **Broca's Area (area 44, 45):** is found on the inferior third frontal gyrus in the hemisphere that is dominant for language. This area is involved in the coordination or programming of motor movements for the production of speech sounds. Broca's area is also involved in syntax which involves the ordering of words, and morphology-the allomorphs at the ends of words e.g., hat+s=hats. Injuries to Broca's area may cause apraxia or Broca's aphasia.
2- The **precentral gyrus**: which may also be called the **primary motor area** (area 4)or, most commonly, the **motor strip** is immediately anterior to the central sulcus. It controls the voluntary movements of skeletal muscles; cell bodies of the **pyramidal tract** are found on this gyrus.
3- The **premotor area** or **supplemental motor area (area 6):** is immediately anterior to the motor strip. It is responsible for the programming for motor movements. It does not, however program the motor commands for speech as these are generated in Broca's area which is also located in the frontal lobe.
4- **Area for conjugate eye movements (Area 8):** is anterior of the premotor cortex. It facilitates eye movements and is involved in visual reflexes as well as pupil dilation and constriction.
5- **Areas 9**, **10**, and **11** are anterior to area **8**. They are involved in cognitive processes like reasoning and judgment which may be collectively called biological intelligence including executive function.
6- **Paracentral lobule:** on the medial surface, concerned with higher control on micturition centers.

7- **Prefrontal cortex**: the most anterior part of the frontal lobe is involved in complex cognitive processes like reasoning and judgment. Also involved in executive function that regulates and directs cognitive processes, decision making, problem solving, learning, reasoning and strategic thinking.

II) The **Parietal Lobe** is immediately posterior to the central sulcus. It is anterior to the occipital lobe, from which it is not separated by any natural boundary. Its inferior boundary is the posterior portion of the lateral fissure which divides it from the temporal lobe.

The parietal lobe is associated with sensation, including the sense of touch, kinesthesia, perception of warmth and cold, and of vibration. It is also involved in writing and in some aspects of reading.

1- The **postcentral gyrus** which is also called the **primary sensory area (area 1, 2, 3)** or the sensory strip is immediately posterior to the central sulcus. This area receives sensory feedback from joints and tendons in the body and is organized in the same manner as the motor strip.
2- **Sensory association areas (Areas 5, 7, and 40):** are found posterior to the primary sensory strip and are considered presensory association areas where somatosensory processing occurs. These areas are capable of more detailed discrimination and analysis than is the primary sensory area. They might, for example, be involved in sensing **how** hot or cold something is rather than simply identifying it as hot or cold.
3- The **angular gyrus (area 39):** lies near the superior edge of the temporal lobe, immediately posterior to the supramarginal gyrus. It is involved in the recognition of visual symbols. Fibers of many different types travel through the angular gyrus, including axons associated with hearing, vision, and meaning. The arcuate fasciculus, the group of fibers connecting Broca's area in the frontal lobe to Wernicke's area in the temporal lobe also connects to the angular gyrus. The following disorders may result from damage to the angular gyrus in the hemisphere that is dominant for speech and language: anomia, alexia with agraphia, left-right disorientation, finger agnosia, and acalcula.

III) The **Temporal Lobe** is inferior to the lateral fissure and anterior to the occipital lobe. It is separated from the occipital lobe by an imaginary line rather than by any natural boundary.

The temporal lobe is associated with auditory processing and olfaction. It is also involved in semantics, or word meaning.

1- **Wernicke's Area (area):** located on the posterior portion of the superior temporal gyrus in the hemisphere that is dominant for language. This area plays a critical role in the ability to understand and produce **meaningful** speech. A lesion here will case Wernicke's aphasia.
2- **Heschl's** Gyrus **(area 41) (primary auditory area):** is the area in the temporal where sound first reaches the brain. It is is also known as the anterior transverse temporal gyrus. There are two **secondary auditory** or **auditory association areas** (area 42, 21 and 22) which make important contributions to the comprehension of speech. They are part of **Wernicke's** area.
3- **Area 42:** immediately inferior to area 41 and is also involved in the detection and recognition of speech. The processing done in this area of the cortex provides a more detailed analysis than that done in area 41.
4- **Areas 21** and **22** are the auditory association areas.
5- **Supramarginal gyrus (Area 37):** is found on the posterior-inferior part of the temporal lobe. Lesions here can cause anomia.

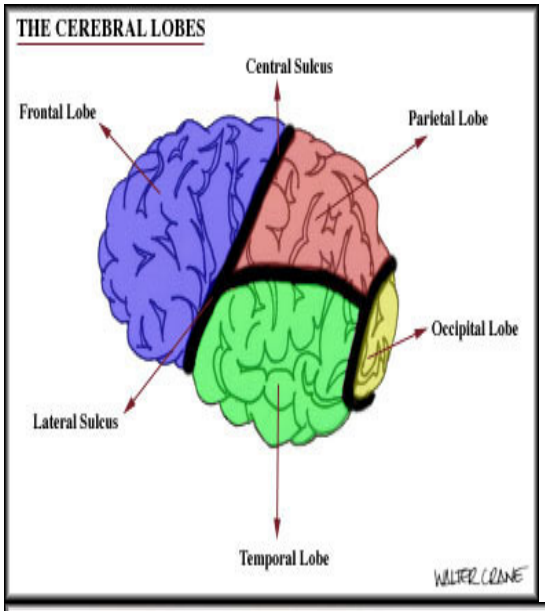
IV) The **Occipital Lobe**: which is the most posterior lobe has no natural boundaries on its lateral aspect. It is involved in vision.

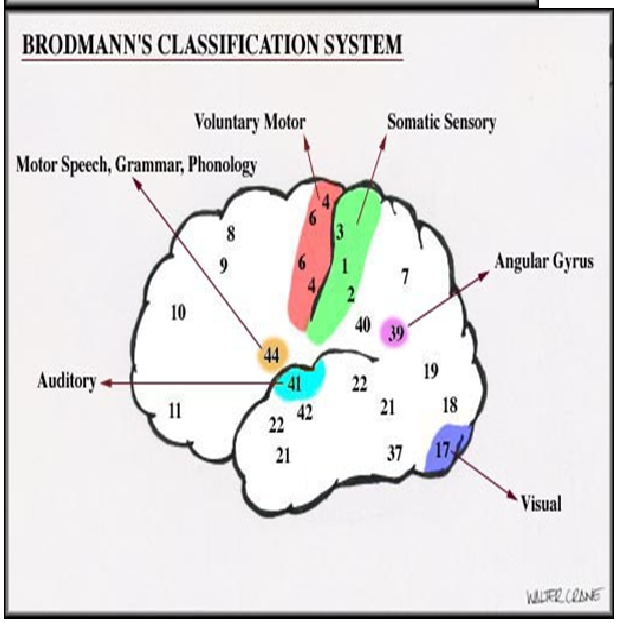
1- The **primary visual area** (area 17): receives input from the optic tract via the thalamus.
2- The **secondary visual areas (area 18, 19):** integrate visual information, giving meaning to what is seen by relating the current stimulus to past experiences and knowledge. A lot of memory is stored here. These areas are superior to the primary visual cortex.

Damage to the primary visual area causes blind spots in the visual field, or total blindness, depending on the extent of the injury. Damage to the secondary visual areas could cause **visual agnosia**.

People with this condition can see visual stimuli, but cannot associate them with any meaning or identify their function.

V) The **Insula** is a cortical area which lies below the fissure of Sylvius, it may be involved in programming for speech for speech sounds.





III) Motor function (Motor system):

- Motor system includes:

    1- Pyramidal (corticosoinal)tract.
    2- Extrapyramidal system.

3- Cerebellum.

A. Corticospinal tract (pyramidal)

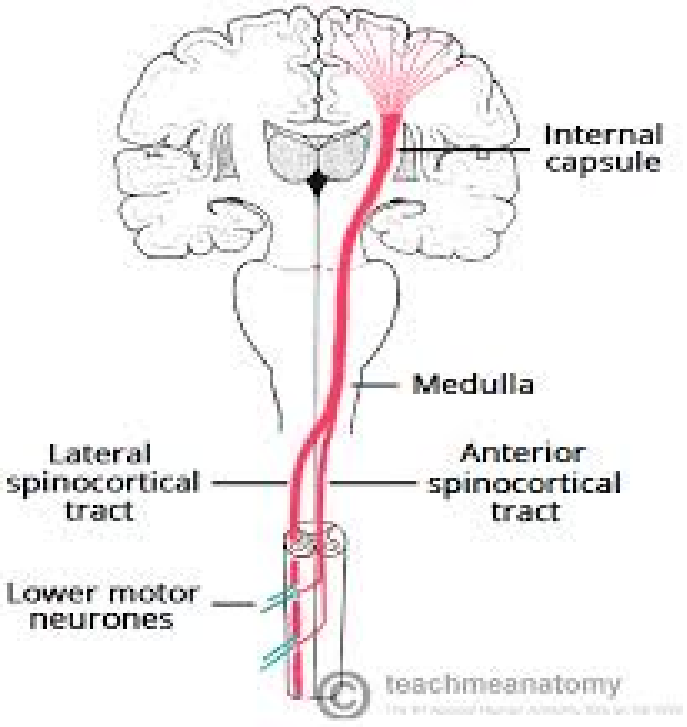
- From motor cortex to medulla as follow:

  - 30% from the motor cortex.
  - 30% from the premotor and supplementary cortex.
  - 40% from somatosensory areas.

<u>- Divided into:</u>

1.Crossed (lateral corticospinal tract): 90% of the fibres.

2.Uncrossed fibers (anterior corticospinal tract): 10% of the fibres.

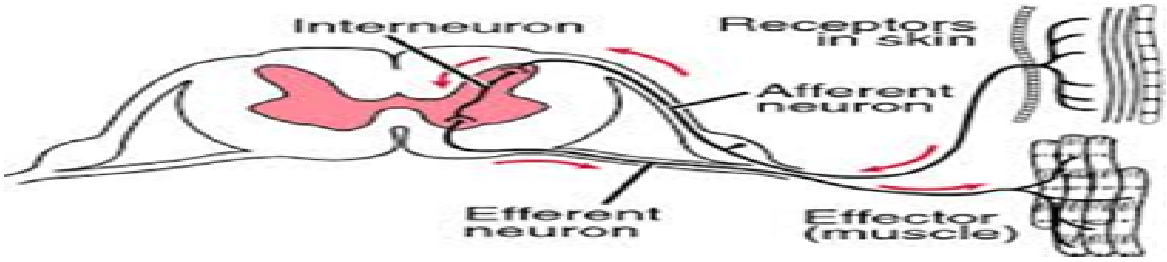


- As corticospinal axons descend from the cortex, they course through the internal capsule (occupying the the genu and the anteriot 2/3 of the posterior limb), the cerebral peduncle of the midbrain, and the ventral pons and onto the ventral surface of the medulla as the pyramids.
- When corticospinal axons reach the medulla they lie within the pyramids as corticospinal tract.

- At the most caudal pole of the pyramids the corticospinal axons cross over the midline and now continue their descent on the contralateral (to the cell of origin) side.
- This crossover point is called the PYRAMIDAL DECUSSATION.
- The crossing fibers enter the lateral funiculus of the spinal cord where they are called the LATERAL CORTICOSPINAL TRACT.
- LCST axons exit the tract to terminate upon neurons in the spinal cord gray matter along its entire length called anterior horn cells (AHCs) where its axon form the peripheral nerve that reach the target muscle.
- All the neurons contributing to the pyramidal and extrapyramidal systems should be called **upper motor neurons (UMN)**.
- The anterior horn cells and the related neurons in the motor nuclei of some cranial nerves are called **lower motor neurons (LMN)**.

LMNL	**UMNL**	**Basis of Difference (STORM Baby)**
Lowers	Lowers	S = Strength
Decreases (flaccid)	Increases (spastic)	T = Tone
- Fasciculations - Fibrillations - Reaction of degeneration	-Superficial reflexes absent -Clonus	O = Others
Decreased	Increased Pathological reflexes may appear	R = Reflexes = DTR or Deep tendon reflexes
Decreases / Atrophy	Slight loss only	M = Muscle Mass
Negative (toe down)	Positive (toe up)	Baby = Babinski Sign

Muscle tone and reflex:



Muscle reflex	Muscle tone	
Induced local axon reflex	Spontaneous local axon reflex	Nature
Tapping of muscle tendon	Stretch of the muscle (as length of muscle is shorter than distance between origin and insertiom)	Stimulus
Golgi tendon	Muscle spindle (in the fleshy muscle fibers)	Receptor
The same	Excite afferent sensory nerve to DRG to AHC	pathway
Brief muscle contraction	Continuous subtetanic (partial) muscle contraction	Response
	Muscle nourishment and body posture	Function

Extrapyramidal System

- The pyramidal system was the primary pathway for voluntary movement.
- The extrapyramidal system is another motor system that is important for control of movements.
- Neuronal activity for this motor system begins in the cerebral cortex and ultimately exerts an influence on the lower motor neurons.
- The pathways are indirect, as opposed to the direct pathways of the pyramidal system.
- The long axons of the corticospinal tract and corticobulbar tract make only one synapse with the lower motor neuron, so the pyramidal system is called monosynaptic.
- The extrapyramidal system, however, is polysynaptic.

❖ The major extrapyramidal nuclei are the **basal ganglia**.

❖ Remember that the basal ganglia is composed of the **Globus Pallidus, Putamen, and Caudate Nucleus**.
❖ Together, the Globus Pallidus and Putamen are called the **Lenticular Nucleus**.
❖ Together, all three are called the **Corpus Striatum**.
❖ Other structures related to the extrapyramidal system include the **substantia nigra**, **red nucleus**, **subthalamic nucleus**, and **reticular formation** of the mesencephalon.
❖ The **cerebellum** is also thought of as contributing to the extrapyramidal system.

- The extrapyramidal system works by **modifying** neural impulses that originate in the cerebral cortex.
- Impulses generated at the primary motor strip are sent via the extrapyramidal fibers to the basal ganglia.
- In a complex network of pathways, the structures of the basal ganglia modify impulses and send information to each other.
- Some fibers will then be directed down to synapse with the lower motor neurons.
- Other fibers are routed through the thalamus and back up to the cortex.

✓ <u>The role of the extrapyramidal system includes the following</u>:
✓ (1) selective activation of movements and supression of others
✓ (2) Initiation of movements
✓ (3) setting rate and force of movements
✓ (4) coordinating movements.

☒ Damage to the extrapyramidal system, but especially damage to the basal ganglia, will result in movement disorders known as dyskinesias. Different types of dyskinesias include:

a) **Myoclonus** :

- characterized by involuntary single or repetitive jerks of a body part.
- If the jerks are repetitive, they can be rhythmic or non-rythmic.
- They can be isolated to one muscle group or a number of muscles at the same time.
- These movements can occur spontaneously, but also to stimuli (visual, tactile or auditory).

- Hiccups are a form of myoclonus (brief spasm of diaphragm.).

b) **Tics** :

- these are rapid, repeatingly coordinated or patterned movemetns that are under partial control by the affected person.
- Often, the person will relate that they have an irresistible urge to perform the movements.
- They can often supress the movements temporarily.
- Simple tics may appear similar to dystonia or myoclonus.
- Complex tics are coordinated and can involve jumping, noises, lip smacking, and other rapid, repeated movements.

c) **Chorea**:

- characterized by rapid, involuntary, random, purposless movements of a body part.
- Can be present at rest, during sustained postures, and during movement.
- Can be subtle or obvious.
- These movements can often be modified by the person after initial onset so that they are made to appear intentional in order to cover them up.

d) **Ballism** :

- characterized by gross, abrupt contractions of axial and proximal muscles of the extremities that can produce flailing.

e) **Athetosis** :

- A relatively slow, writhing, purposless movement of a body part.
- Athetosis and choreaic movements often combine with eachother, and called choreoathetosis.
- Athetosis is a major category of the effects of Cerebal Palsey.

f) **Dystonia:**

- a slow form of hyperkinesia characterized by involuntary abnormal postures resulting from excessive co-contraction of antagonistic muscles.
- Writers cramp is a form of this.

g) **Spasm** :

- a general term that designates a variety of muscular contractions. Tonic spasms are prolonged.
- Clonic spasms are repetitive, have a rapid onset, and are brief.

h) **Tremor** :

- Rhythmic (periodic) movement of a body part.
- **Resting tremors** occur when a body part is at rest.
- **Postural tremor** occurs when the body part is maintained against gravity.
- **Action tremor** occurs during movement.
- **Terminal tremor** occurs as the body part nears a target. Can be caused by cerebellar circuit problems.

Language And Speech Disorders

(Dr.Hosna Saad)

- **Speech** is the process of articulation and pronunciation. It involves the bulbar muscles and the physical ability to form words.
- **Language** is the process in which thoughts and ideas become spoken. It involves the selection of words to be spoken, called **semantics**, and the formulation of appropriate sentences or phrases, called **syntax**.

Definitions

- **Dysarthria:** is a speech disorder caused by disturbance of muscular control (articulation of speech).
- **Dysphasia**: is an impairment of language (formulation of speech).
- **Apraxia of speech**: is the loss of ability to plan and execute the oral motor tasks needed in order to speak.
- Inability to write is **agraphia** if incomplete. Inability to manipulate numbers is **acalculia** if incomplete. Difficulty reading is **dyslexia**.

• Dysphasia

✓ **Causes:**

Dysphasia is impaired ability to understand or use the spoken word. It is due to a lesion of the dominant hemisphere and may include impaired ability to read, write and use gestures. The most common cause is cerebrovascular disease but it can arise from a space-occupying lesion, head injury or dementia.

Anatomy:

There are several areas of the brain that play a critical role in speech and language.

1- Broca's Area

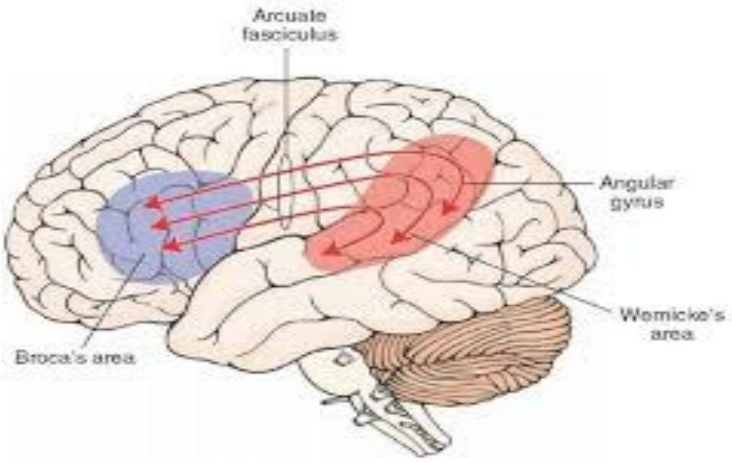
Broca's area, located in the left hemisphere, is associated with speech production and articulation. Our ability to articulate ideas, as well as use words accurately in spoken and written language, has been attributed to this crucial area

2- Wernicke's Area

This critical language area in the posterior superior temporal lobe connects to Broca's area via a neural pathway (Arcuate Fasiculus). Wernicke's area is primarily involved in the comprehension. Historically, this area has been associated with language processing, whether it is written or spoken.

3- Angular Gyrus

The angular gyrus allows us to associate multiple types of language-related information whether auditory, visual or sensory. It is located in close proximity to other critical brain regions such as the parietal lobe which processes tactile sensation, the occipital lobe which is involved in visual analyses and the temporal lobe which processes sounds. The angular gyrus allows us to associate a perceived word with different images, sensations and ideas.



Features of dysphasia

The diagnosis of dysphasia is made only after excluding sensory impairment of vision or hearing, perceptual impairment (agnosia), cognitive impairment (memory), impaired movement (apraxia) or thought disturbance, as in dementia or schizophrenia.

Types:

Specific types of dysphasia are associated with damage to particular cortical regions. Generally, expressive dysphasia suggests an anterior lesion while receptive dysphasia suggests a posterior lesion. There are several subtypes. They are:

1- Broca's (expressive or motor) aphasia:

Due to damage to Broca's area (area 44) of the language-dominant hemisphere. People with expressive dysphasia are not fluent and have difficulty forming words and sentences. There are grammatical errors and difficulty finding the right word. In severe cases they do not speak spontaneously but they usually understand what is said to them.

2- Wernicke's (receptive or sensory) aphasia:

Due to damage to the posterior superior areas of the language dominant temporal lobe (often called Wernicke's area). People with receptive dysphasia often have language that is fluent with a normal rhythm and articulation but it is meaningless as they fail to comprehend what they are saying.

This pattern of receptive aphasia is marked by:

- Fluent, grammatically correct speech with little meaning
- Poor comprehension
- Paraphasic errors:
    - calling a spoon a "fork" (semantic)
    - calling a spoon a "spood" (literal)
- Neologisms (or nonsense words)

3- Conduction dysphasia/aphasia

Lesions are around the arcuate fasciculus, posterior parietal and temporal regions. Symptoms are naming deficits, inability to repeat non-meaningful words and word strings, although there is apparently normal speech comprehension and production. Patients are aware of their difficulties.

4- Transcortical sensory dysphasia/aphasia:

Lesions are in the junction areas of the temporal, parietal and occipital areas of left hemisphere. Symptoms are impaired comprehension, naming, reading, writing and semantic irrelevancies in speech.

5- **Transcortical motor dysphasia/aphasia**:

Lesions are located between Broca's area and supplementary motor area. Symptoms are transient mutism, telegrammatic, and dysprosodic speech. Telegrammatic means omitting unimportant words, as was done when sending a telegram. Dysprosodic speech is monotone.

6- Global aphasia

If damage encompasses both Wernicke's and Broca's areas, global aphasia can occur. In this case, all aspects of speech and language are affected. Patients can say a few words at most and understand only a few words and phrases. They usually cannot carry out commands or name objects. They cannot read or write or repeat words said to them.

Dysarthria

Causes of dysarthria

Dysarthria is caused by upper motor neuron lesions of the cerebral hemispheres or lower motor neuron lesions of the brain stem. It also results from disruption to the integrated action of upper motor neurones, basal ganglia and cerebellum.

Types of dysarthria

There may be some variation depending upon the site of the lesion

- Slurred speech: due to upper motor neuron lesion.
- Staccato speech: caused by cerebellar lesions.
- Scanning speech: caused by mixed pyramidal amd cerebellar lesions.
- Monotonous voice is caused by disease of the extrapyramidal system in Parkinson's disease..

- Nasal tonation: indistinct articulation, hypernasality and bilateral weakness caused by lower motor neurone disorders can occur with motor neurone disease.

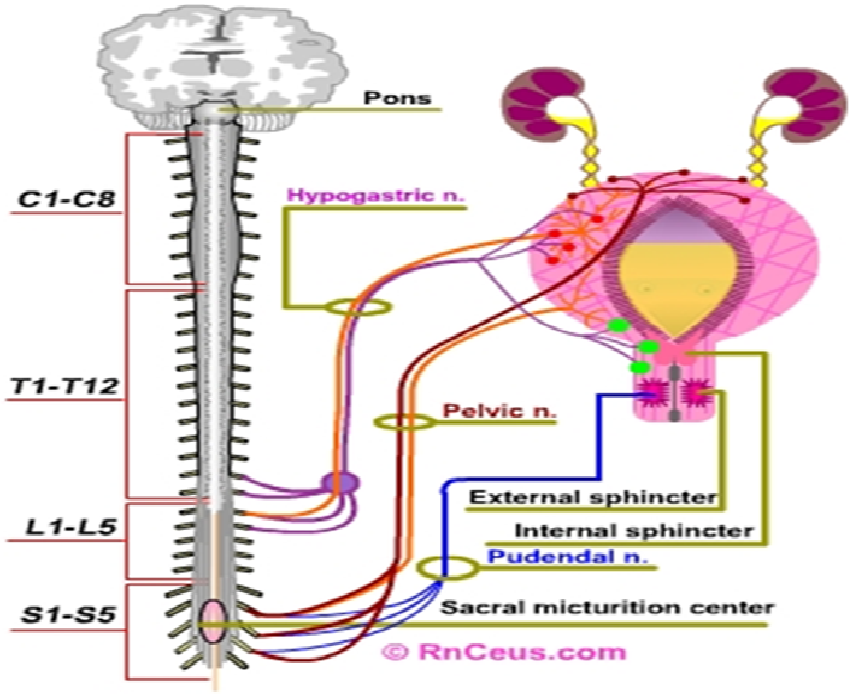
Urinary System: Normal Anatomy & Physiology

- Afferent information on the state of bladder filling is transmitted from sensory fibers that run in the pelvic nerves to the sacral dorsal root ganglia, and after transduction of these signals in the dorsal horn of the spinal cord, this sensory information is transmitted to the **periaqueductal gray (PAG)** matter where it is then relayed via the hypothalamus and thalamus to the **cortical areas** (anterior cingulate cortex, insula, and prefrontal cortex). This allows voluntary control of micturition by modulating the activity of the PAG, which itself has excitatory input to the pontine micturition center (PMC).
- The **pontine micturition center (PMC)** is essential for the co-ordination of micturition. This is accomplished by the PMC modulating the opposing effects of the parasympathetic and sympathetic nervous systems on the lower urinary tract.
- Three mixed sensory and motor nerves (hypogastric, pelvic, and pudendal nerves) innervate the lower urinary tract.

1- The **hypogastric nerve** carries **sympathetic** autonomic nervous system innervation, it a rises from T11-L2 cord leve l. Activation of the thoraco-lumbar sympathetic outflow results in detrusor relaxation and bladder neck (internal s phincter) contraction.

2- The **pelvic nerve** carries the **parasympathetic** autonomic nervous system innervation. It arises from the detrusor nucleus at the S2–S4 cord level. Activation of the sacral parasympathetic outflow results in detrusor contraction and relaxation of the proximal urethra.

3- The **pudendal nerve** carries the **somatic** nervous system innervation to the lower urinary tract. It arise from the pudendal (O nuf 's) nucleus at S2–S4 cord level to supply the external urethral sphincter striated muscle. Supra-spinal centers, which normally are under voluntary control, produce excitatory influence on the pudendal nucleus during the bladder filling stage to produce external urethral sphincter and pelvic floor contraction to help maintain continence.



So during the bladder filling stage, supraspinal centers produce inhibition of the pontine micturition center, which results in enhancement of thoraco-lumbar sympathetic outflow with simultaneous suppression of sacral parasympathetic outflow to the lower urinary tract. These supraspinal centers also produce excitatory outflow through the pudendal nerve to produce external urethral sphincter contraction. The overall effect in normal bladder physiology is detrusor smooth muscle relaxation, bladder neck smooth muscle and external urinary sphincter skeletal muscle contraction that allow low pressure storage of urine in the bladder without leakage. And the opposite occur during the bladder emptying phase.

Pathophysiology of Neurogenic Bladder

Classifications of neurogenic bladder dysfunction:

1- In **uninhibited neurogenic bladder** dysfunction (Lesion above the pons):

- Urinary incontinence may occur with brain lesions occurring above the pontine micturition center, especially with bilateral lesions.
- Signs of urge incontinence or spastic bladder (termed detrusor muscle hyperreflexia). Bladder usually empties too quick and too often with relatively small quantities.
- Usually associated with impotence.
- Since the PMC is intact, the normal opposition of detrusor and internal/external sphincter tonus is maintained so there are no high bladder pressures developed that can lead to upper urinary tract damage. Also no residual volume so no risk of infection.

2- **Spinal cord lesion (Automatic bladder)**:

- There is urge incontinence like above lesion.
- It is characterized by **detrusor-sphincter dyssynergia** (DSD), where in simultaneous detrusor and urinary sphincter contractions produce high pressures in the bladder (up to 80–90 cm H2O) leading to vesico-ureteral reflux that can produce renal damage.
- If detrusor pressure exceeds internal/external urinary sphincter pressure in the proximal urethra, then incontinence may occur.

3- **Sensory atonic bladder**: lesion in the afferent fibres, with absence sense of fullness of the bladder. The bladder is large and

has low pressure producing urinary retention with overflow dribbling.

4- **Motor atonic bladder**: lesion in the pudendal nucleus or nerve. there is preservation of sense of fullness of the bladder but there is retention of urine with inability to evacuate the bladder voluntarily.

5- **Sacral cord lesion (Autonomic bladder)**: In lower motor neuron neurogenic bladder, the sacral micturition centers or related peripheral nerves are damaged though the thoracic sympathetic nervous system outflow to the lower urinary tract is intact. The bladder capacity is large since detrusor tone is low (detrusor areflexia) and internal urinary sphincter innervation is intact. Despite the low detrusor pressure, over flow urinary incontinence and urinary tract infections are not uncommon.

Vascular Diseases Of The Nervous System

(Cerebrovascular Stroke)

(Dr Mostafa Melek)

Stroke is a major public health problem, being the third most common cause of death after myocardial infarction and cancer, and the leading cause of adult disability.

Definition:

- Stroke can be briefly defined as an acute focal neurological deficit resulting from vascular disease.
- **The WHO definition**: (Rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer, or leading to death, with no apparent cause other than of vascular origin).

Physiology:

- The adult brain, which weighs about 1500 gm or 2% of the total body weight, requires an uninterrupted supply of about 150 gm of glucose and 72 L of oxygen every 24 hours, accounting for 20% of the total body oxygen consumption.
- As the brain does not store these substances, dysfunction results after only a few minutes of deprivation when either the oxygen or the glucose content is reduced below critical levels.
- In the resting state, a normal total cerebral blood flow is 50 mL/min per 100 g.

Pathogenesis And Classification:

Brain Infarction

- Brain or neuronal dysfunction occurs at cerebral blood flow levels of below 50 mg/dL, and irreversible neuronal injury is initiated at levels below 30 mg/dL.
- When blood supply is completely interrupted for 30 seconds, brain metabolism is altered.
- After 1 minute, neuronal function may cease. After 5 minutes of interruption, anoxia initiates a chain of events that may result in cerebral infarction; however, if oxygenated blood flow is restored quickly enough, the damage may be reversible, as with a TIA.

Modifiable Risk Factors That May Increase the Probability of Stroke

Modification	***Risk Factors***
Antihypertensives, Diet	***Hypertension***
Antiplatelets	***Heart disease***
Anticoagulants, Antiarrhythmics	***Atrial fibrillation***
Glucose and blood pressure control	***Diabetes mellitus***
Diet, lipid-lowering medication	***Hypercholesterolemia***
Routine exercise	***Physical inactivity***
Cessation	***Smoking***
Quantity reduction	***Heavy alcohol use***
Antiplatelets, endarterectomy, angioplasty	***Asymptomatic carotid stenosis***
Antiplatelets, endarterectomy	***Transient ischemic attack***

Transient Ischemic Attack:

<u>Definition:</u>

Transient ischemic attack (TIA) describes neurologic symptoms of ischemic origin that last less than 24 hours. In fact, most attacks last only a few minutes to an hour.

causes:

- When severe major carotid or vertebrobasilar stenosis is present, transient thrombosis could be operative; such TIAs tend to be brief.
- Attacks without severe stenosis tend to last longer and often are associated with distal branch occlusion, suggesting embolism from an ulcerated plaque or a more proximal source.
- Some TIAs, especially vertebrobasilar, may have a hemodynamic basis, including transient hypotension and cardiac arrhythmia, and TIAs responsive to calcium-channel blockers suggest a vasospasm basis.
- Other TIAs may be a consequence of primary, intraparenchymal vascular disease.
- Fibromuscular dysplasia of the basilar artery and dissection of the middle cerebral artery.
- TIAs have also been associated with anemia, polycythemia, hyperviscosity, thrombocythemia, cerebral venous thrombosis, bacterial endocarditis, and temporal arteritis, and may clear with correction of the underlying disorder.

Signs And Symptoms of TIA:

Symptoms vary with the arterial territory involved.

- Transient monocular blindness (amaurosis fugax): reflecting ischemia in the territory of the central retinal, consists of blurring or darkening of vision, peaking within a few seconds (sometimes as if a curtain had descended), and usually clearing within minutes.

- Limb weakness and
- sensory loss,
- aphasia,
- hemineglect, and
- homonymous hemianopia.
- Posterior circulation TIAs cause symptoms referable to the cerebrum (visual field loss or cortical blindness), brainstem (cranial nerve and long tract symptoms, sometimes crossed or bilateral), and cerebellum.

Recurrent TIAs of the same type are more likely to be the result of critical narrowing of the involved artery than of embolism.

Diagnosis:

- The differential diagnosis of TIAs includes migraine, cardiac arrhythmia, seizures, hypoglycemia, compressive neuropathy, conversion, and neurosis.
- Although TIAs are defined in terms of their clinical reversibility, and are presumed to signify ischemia too brief or incomplete to cause infarction, imaging frequently demonstrates appropriately located infarcts. Some investigators therefore believe that the definition of TIA should be changed to indicate brief episodes typically less than one hour without evidence at imaging of acute infarction.

- Fifteen percent of ischemic strokes are preceded by a TIA.
- After a first TIA, 10% to 20% of patients have a stroke within the next 90 days, and in half of them, the stroke occurs within the first 48 hours after the TIA.

Localization of the Occluded artery

Syndrome	*Artery Occluded*
Asymptomatic	**Common carotid**
Ipsilateral blindness	**Internal carotid**
Contralateral hemiparesis and hemianesthesia	
Hemianopia	
Aphasia or denial and hemineglect	
	Middle cerebral
Hemiplegia	Main trunk
Hemianesthesia	
Hemianopia	
Aphasia or denial and hemineglect	
Hemiparesis and sensory loss (arm and face more affected than leg)	Upper division
Broca aphasia or denial and hemineglect	
Wernicke aphasia or nondominant behavior disorder without hemiparesis	Lower division
Pure motor hemiparesis	Penetrating artery
Hemiparesis and sensory loss affect leg more than arm	**Anterior cerebral**
Impaired responsiveness (abulia or akinetic mutism), especially if bilateral infarction	
Left-sided ideomotor apraxia or tactile anomia	
Cortical, unilateral: isolated hemianopia (or quadrantic field cut); alexia or color anomia	**Posterior cerebral**
Cortical, bilateral: cerebral blindness, with or	

without macular sparing

Thalamic: pure sensory stroke; may leave anesthesia dolorosa with spontaneous pain

Subthalamic nucleus: hemiballism

Bilateral inferior temporal lobe: amnesia

Midbrain: oculomotor palsy and other eye-movement abnormalities

Signs That Indicate the Level of Brainstem Vascular Syndromes

Manifestations	***Structure***	***Artery Affected***	***Syndrome***
			Medial
Ipsilateral	Emerging	Paramedian	Medulla
Paralysis of gaze to	Pontine gaze	Paramedian	Inferior pons
Ipsilateral abduction	Emerging		
Internuclear	Medial	Paramedian	Superior

	fasciculus		
			Lateral syndromes
Dysphagia, hoarseness, ipsilateral paralysis of vocal cord; ipsilateral loss of pharyngeal reflex	Emerging fibers of 9th and 10th nerves	Posterior inferior cerebellar or vertebral artery branches	Medulla
Vertigo, nystagmus	Vestibular nuclei		
Ipsilateral facial analgesia	Descending tract and nucleus of fifth nerve		
Taste loss on ipsilateral half of tongue posteriorly	Solitary nucleus and tract		
Ipsilateral facial paralysis	Emerging fibers of seventh nerve	Anterior inferior cerebellar	Inferior pons
Taste loss on ipsilateral half of tongue anteriorly	Solitary nucleus and tract		
Deafness, tinnitus	Cochlear nuclei		

Ipsilateral jaw weakness	Motor nucleus of fifth nerve		Mid-pons
Ipsilateral facial numbness	Emerging sensory fibers of fifth nerve		

Intracerebral Hemorrhage

Etiologic Factors for Intracerebral Hemorrhage

Demographic

Age

Race/Ethnicity

Vascular Risk Factors

Chronic Hypertension (small vessel disease)

Alcohol

Smoking

Low Cholesterol

Cerebral	metastasis
Inflammatory	
Vasculitis	(cerebral, systemic)
Endocarditis	(mycotic aneurysm)
Hematologic	
Coagulopathy	
Thrombocytopenia	
Iatrogenic	
Anticoagulants	
Fibrinolysis	
Toxic	
Cocaine	
Amphetamines	

- Most hemorrhages in the brain parenchyma arise in the region of the small arteries that serve the basal ganglia, thalamus, and brainstem and are caused by an arteriopathy of chronic hypertension or microatheroma.
- Other well established risk factors for intracerebral hemorrhage include increasing age, cigarette smoking, alcohol consumption, and low serum cholesterol. Brain tumors, sympathomimetic drugs, coagulopathies, cavernomas and arteriovenous malformations also cause brain hemorrhages.
- Because most spontaneous hemorrhages arise from tiny vessels, the accumulation of a hematoma takes time and explains the smooth onset of the clinical syndrome over minutes or hours.

- Compared with the violence of hemorrhage from aneurysm, terms like rupture rarely apply.
- The progressive course, frequent vomiting, and headache are major points that help to differentiate hemorrhage from infarction.
- Hemorrhage usually stops spontaneously by 30 minutes but in fatal cases, continues until death is caused by brain compression or by disruption of vital structures.
- The putamen is the site most frequently affected. When the expanding hematoma involves the adjacent internal capsule, there is a contralateral hemiparesis, usually with hemianesthesia and hemianopia and in large hematomas, aphasia or impaired awareness of the disorder.
- However, small self-limiting hematomas close to the capsular region may occasionally mimic lacunar syndromes featuring pure motor or sensory deficits.
- When the hemorrhage arises in the thalamus, hemianesthesia precedes the hemiparesis.
- Pontine hemorrhage usually plunges the patient into coma with quadriparesis and grossly disconjugate ocular motility disorders, although small hemorrhages may mimic syndromes of infarction.
- In the cerebral lobes, white matter hematomas often result from arteriovenous malformations, amyloid angiopathy, tumors, or other causes that only uncommonly affect the basal ganglia, thalamus, and pons.

- Cerebellar hemorrhage warrants separate description because the mode of onset differs from that of cerebral hemorrhage and because it often necessitates surgical evacuation.

- The syndrome usually begins abruptly with vomiting and severe ataxia (which usually prevents standing and walking); it is occasionally accompanied by dysarthria, adjacent cranial nerve (mostly sixth and seventh) affection, and paralysis of conjugate lateral gaze to one side.

Other Cerebrovascular Syndromes

❖ ***LACUNAR STROKES***

- Lacunar strokes are syndromes associated with discrete occlusion of penetrating arterioles (less than 500 µm diameter), most frequently due to sustained hypertension and causing cystic degeneration of brain due to tissue infarction.
- The symptoms depend on the location of the small infarcts, but may be silent with no meaningful symptoms.
- The pathology from sustained hypertension is defined as lipohyalinosis, although the pathophysiology is uncertain.
- ***The most common lacunar syndromes are the following***:
    1. pure motor hemiplegia, usually involving face and limbs on the side opposite the infarct;
    2. pure hemisensory stroke, usually in the same pattern as the pure motor lacunar stroke;
    3. ipsilateral ataxia and hemiparesis; and
    4. the dysarthria-clumsy-hand syndrome.

Usually, the prognosis for the lacunar syndrome is good, provided the expected hypertension is controlled.

❖ ***HYPERTENSIVE ENCEPHALOPATHY***

- This condition, like so-called malignant hypertension, is a medical emergency requiring immediate hypotensive therapy (rapid acting agents preferably, such as intravenous labetalol, nicardipine, sodium nitroprusside, hydralazine, and sometimes angiotensin converting enzyme (ACE) inhibitors) to minimize serious neurological complications such as strokes, but care must be made not to reduce the mean arterial pressure (MAP) below the level of autoregulation or as an initial mean arterial pressure (MAP) reduction by 15% to 20%.
- Otherwise, watershed or border-zone infarcts may result because flow is dependent upon pressure alone.
- patients with hypertensive encephalopathy usually have diastolic blood pressures of greater than 140 mmHg (except in toxemia/eclampsia and in children with initial blood pressure usually much lower than adult men)
- the patients display encephalopathic symptoms such as confusion, drowsiness, seizures, as well as blurring of vision and headache, but no focal neurologic signs.
- Fundi frequently show hemorrhages, exudates and disc edema, and Grade IV Keith-Wagner changes.
- Brain MRI may show posterior leukoencephalopathy with decreased T1- and increased T2-white matter signal because of breakthrough which causes diapedesis of serum through the blood brain barrier. With reduction of MAP, the patient sensorium frequently clears, a sign that is diagnostic for hypertensive encephalopathy.

❖ ***FIBROMUSCULAR HYPERPLASIA***

- Fibromuscular bands of uncertain etiology form segmental narrowing of large arteries such as the carotid artery, and the bands may provoke platelet adhesion and thereby cause transient ischemic attacks or infrequently thromboembolic strokes.
- Most frequently they present with asymptomatic carotid bruits or are seen incidentally, during a cerebral angiogram and has the appearance of a string of pearls.
- If the renal artery is involved, patients may develop hypertension; bruits may be heard over the renal artery.
- Antiplatelet drugs, anticoagulation, and angioplasty have been reported to reduce the frequency of TIAs in patients presenting with them.

Stroke in Young Adults, causes:

- CADASIL: Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy
- Dissection (traumatic or spontaneous)
- Fibromuscular Dysplasia
- Migraine
- MELAS, mitochondrial encephalopathy with lactic acidosis and stroke-like events
- Moyamoya syndrome
- Oral contraceptive use, including low-dose estradiol pills
- Venous occlusive diseases

Cardiogenic emboli

- Anatomic abnormalities and atherosclerosis patent foramen ovale (PFO); mitral valve prolapse, with redundancy of the mitral leaflet; valvular replacement; & cardiomyopathies post-myocardial infarction, and alcoholic; endocardial fibrosis; aortic atheromas without)
- Arrhythmias (especially atrial fibrillation and sick-sinus syndrome)
- Immunecomplex disorders and paraneoplastic syndromes (Libman-Sacks Syndrome with systemic lupus erythematosus; nonbacterial thrombotic endocarditis or marantic endocarditis, seen in AIDS and with neoplasms, occult and otherwise)
- Infections (bacterial endocarditis; viral cardiomyopathy; rheumatic heart disease
- Tumors (atrial myxoma)

Blood elements

- Erythrocytes (sickle cell disease; polycythemia vera)
- Platelets (thrombocytosis, usually >1 million/cmm; thrombotic thrombocytopenia purpura)
- Proteins (resistance to protein C activation, Factor V-Leiden; antiphospholipid syndrome, Sneddon syndrome; Waldenstrom macroglobulinemia)
- Coagulation defects (deficiency of protein C, S and Antithrombin III, alcohol-induced prothrombotic state; paroxysmal nocturnal hemoglobinuria; plasminogen-activator inhibitor-1, PAI-1 polymorphism; prothrombin polymorphism)

Treatment and Prevention of Strokes

- Therapies for stroke management and prevention are designed to: (1) minimize or prevent stroke occurrence, (2) optimize functional recovery following strokes, and (3) avert stroke recurrences. Specific measures for treatment and prevention depend upon the stroke syndrome being considered.
- Stroke syndromes are conveniently divided by neuroimaging findings and are classified as either ischemic or hemorrhagic.
- With ischemic strokes, the primary causes are atherothrombotic, with artery-to-artery thromboembolism and cardioembolic strokes with other causes from prothrombotic conditions noted above.
- Treatment and prevention will be directed primarily to atherothrombotic brain infarction (ABI) and cardioembolic strokes.

- Hemorrhagic strokes are categorized as: subarachnoid hemorrhages, primarily arising from berry or congenital aneurysms but may also be the result of a variety of arteriovenous malformations; and intracerebral hemorrhage, most commonly caused by sustained hypertension, but may occur with hypocoagulable states as well as either primary or metastatic tumors in the brain

ATHEROTHROMBOTIC STROKES AND TIAS

- ABI, usually with artery-to-artery thromboembolism, is the most common stroke syndrome; it results from atherosclerotic lesions that are primarily extracranial in white populations, while primarily intracranial in African American and Asian people.
- The syndromes of ABI form a continuum from TIAs to completed infarction with fixed neurologic deficits.
- Whether an intermediate condition of stroke-in-evolution or progressing stroke exists is controversial.
- Thrombosis on an atherosclerotic plaque may occur for several pathologic reasons. **The first** of these, and most common, is rupture of the plaque that stems from a high concentration of cholesterol-esters, foam cells, and inflammatory constituents that make the plaque unstable.
- For TIAs caused by carotid stenosis of equal to or greater than 70% by diameter, carotid endarterectomy (CEA) by a skilled surgeon with an acceptable track record is the treatment of choice over medical therapy, in good surgical candidates.
- Efforts to determine the value of angioplasty and stents is being

investigated, both for extra- and intracranial stenosis.

- To prevent TIA recurrence and the potentials for a completed stroke in subjects with TIAs or minor strokes caused by extra- or intracranial occlusive disease, antiplatelet drugs such as aspirin have been effective.

- Studies on the benefits of aspirin show a reduction of strokes by approximately 25%.
- The optimum dose of daily aspirin, whether ultra-low doses at 30 to 75 or 80 mg to high doses of 1,300 mg remains controversial, but low doses appear effective and have less side effects such as gastrointestinal bleeding.
- The action of aspirin is to acetylate irreversibly and inhibit platelets cyclooxygenase I, which thereby stops synthesis of the powerful platelet aggregant thromboxane A_2 (TXA2).
- Lower doses of aspirin have the advantage of minimizing inhibition of endothelial cells production of prostacyclin (PGI2), the powerful platelet antiaggregant.
- Newer anti-platelet drugs, which blunt the GP IIbIIIa receptor which is involved in platelet adhesion, appear to operate synergistically with aspirin in potentiating aspirin anti-aggregant effects; these drugs are ticlopidine and clopidogrel and dipyridamole in combination with aspirin. Clopidogrel, an analog of ticlopidine, has fewer side effects such as diarrhea, bruising and leucopenia which require frequent monitoring when using ticlopidine.
- Dipyridamole plus aspirin may be the best combination to

reduced recurrent TIAs or ischemic strokes following TIAs.

- Aspirin and clopidogrel increases bleeding so this combination should be avoided for chronic therapy.

COMPLETED STROKES WITH FIXED NEUROLOGIC DEFICITS

- For patients with ischemic strokes caused by ABI or cardiogenic emboli, who had a negative CT or MRI of brain for bleeding and minimal infarction, and who were seen within 3 hours of onset of symptoms, the thrombolytic agent, tissue plasminogen activator (tPA), was found beneficial. tPA was approved for patient use by the FDA in 1996.

Tissue Plasminogen Activator (tPA) Exclusion Criteria

Stroke or head trauma within the preceding 3 mths
Major surgery within the preceding 2 wks
History of intracerebral hemorrhage

Blood glucose >400 mg/dL (21.6 mmol/L)
Patients requiring very aggressive therapy attempts for blood pressure reduction

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EMBOLIC STROKES OF CARDIAC AND AORTIC ORIGIN

- Treatment of cardiogenic emboli depends on the offending pathology: -- infected prosthetic valves need replacement, and myxomatous emboli require surgical removal of the tumor.
- The most common cause of cardiogenic emboli (more than 50% of cases) is from arrhythmias, particularly atrial fibrillation, with or without mitral pathology, and recent myocardial infarction (MI).
- Post-MI emboli occur with large, anterior or septal infarcts, particularly those with akinetic segments, as detected by 2D echocardiography.
- Mitral valve prolapse and patent foramen ovale (PFO), both discussed above, occur more commonly in young adults.
- In embolic strokes caused by atrial fibrillation, anticoagulation to reduce embolization is indicated with an international normalized ratio (INR) between 2.0 and 3.0.
- In the Stroke Prevention in Atrial Fibrillation (SPAF) study, anticoagulation reduced stroke recurrence substantially, even in patients over the age of 75 years.
- Chances of embolization are associated with the following risk factors: previous embolization, left ventricular hypertrophy with reduced ejection fraction, sustained hypertension, and congestive failure.

- Aortic atheromas measuring at least 4 mm or more, without calcification, are considered thrombogenic, and anticoagulation to prevent embolization is being investigated for these patients.

INTRACEREBRAL HEMORRHAGE

- Acute treatment of intracerebral hemorrhage includes airway protection, adequate ventilation, and blood pressure levels below a mean arterial pressure of 130 mmHg.
- Fluid balance and body temperature should be maintained at normal levels. Increased intracranial pressure may require osmotherapy, controlled hyperventilation, or barbiturate-induced coma.
- The administration of corticosteroids is generally avoided.
- Apart from cases suffering cerebellar hemorrhage, any decision on whether, how, and when to intervene neurosurgically after intracerebral hemorrhage is subject to current debates and awaits data from ongoing prospective trials.
- To date all clinical trial attempts have failed to show a superiority of hematoma evacuation over medical therapy, save for cerebellar hemorrhage, where surgery for the larger masses may be lifesaving and may be followed by satisfactory clinical outcomes

SUBARACHNOID HEMORRHAGE (SAH)

- Extirpation of the aneurysm is the definitive therapy for aneurysms causing SAH and may be accomplished surgically or with balloons and coagulation techniques, such as with coils deposited in the aneurysm.

- Following SAH and prior to surgery, patients should be sedated and kept in a quiet environment to prevent elevations of blood pressure that may provoke rebleeding, which is a major complication of SAH, along with vasospasm, ventricular dilatation, and Syndromes of Inappropriate ADH Secretions (SIADH).
- Antifibrinolytic agents, such as epsilon-amino-caproic acid, used to preserve the thrombus around an aneurysm thereby preventing rebleeding, have been unsuccessful.
- Vasospasm may be minimized with the calcium channel antagonist, nimodipine, which crosses the blood-brain barrier; intrathecal thrombolytic therapy may be useful in reducing vasospasm. Hydrocephalus may require ventricular shunting.
- Assessment of nitric oxide synthase (eNOS) polymorphism may be of value in predicting whether or not asymptomatic aneurysms are more likely to bleed.

STROKE REHABILITATION

- A team approach for stroke rehabilitation, starting from a stroke recovery unit with experienced physiatrists and physical therapists, has proven beneficial for the optimum recovery of patients
- . This approach is particularly helpful in averting various complications from strokes, such as infections, contractures, and decubiti, and in maximizing independence for patients with hemiplegia/paresis by teaching them to transfer effectively from bed to wheelchair.
- Activities of daily living (ADLs) may be optimized for personal hygiene, dressing, and feeding, as well.

- Depression is a frequent accompaniment of strokes, partially because the reality of a physical disability exists but also because there is altered brain chemistry, which may respond well to selective serotonin-reuptake inhibitors (SSRIs) and tricyclic antidepressants.
- Speech and occupational therapists should be consulted to help patients improve their communication skills and ADL skills.

STROKE PREVENTION

- Stroke prevention depends upon the stroke syndrome and its pathology, such as atherosclerosis, arteritis, cardiac diseases, dissection, and so on, but since atherosclerosis is the most common cause of ischemic strokes, the primary stroke syndrome, only interventions to prevent atherosclerosis will be reviewed here.

- The risk factors for atherosclerosis are well known and require the active involvement of the physician to help patients develop motivational drives to control or stop these risk factors, which include hypertension, smoking, diabetes mellitus, elevated cholesterol, or more correctly, increased low-density lipoprotein (LDL), obesity, sedentary life, and negative stress levels.

Multiple Sclerosis & Other Inflammatory Demyelinating Diseases of the Central Nervous System

(Dr.Ibrahim Alahmar)

- Neurological Diseases with relative preservation of axons, loss of oligodendrocytes, and astroglial scarring.
- Certain clinical features are typical of MS, but the disease has a highly variable pace and many atypical forms.
- Investigative studies are often needed to confirm the diagnosis and exclude other possibilities.
- Advances in disease monitoring and treatment hold promise of slowing the progression of disability.
- Understanding of the basic nature of the disease remains limited, and better control of the disease and repair of damaged CNS tissue remain as goals for the near and more distant future.

❖ Diseases of Myelin

- **AUTOIMMUNE**
  - Acute disseminated encephalomyelitis
  - Acute hemorrhagic leukoencephalopathy
  - Multiple sclerosis
- **INFECTIOUS**
  - Progressive multifocal leukoencephalopathy
- **TOXIC/METABOLIC**
  - Carbon monoxide
  - Vitamin B12 deficiency
  - Mercury intoxication (Minamata disease)
  - Alcohol/tobacco amblyopia
  - Central pontine myelinolysis
  - Marchiafava-Bignami syndrome
  - Hypoxia
  - Radiation
  - **VASCULAR**
  - Binswanger's disease
- **HEREDITARY DISORDERS OF MYELIN METABOLISM**
  - Adrenoleukodystrophy
  - Metachromatic leukodystrophy
  - Krabbe's disease

- Alexander's disease
- Canavan-van Bogaert-Bertrand disease
- Pelizaeus-Merzbacher disease
- Phenylketonuria

❖ PATHOLOGY

- ❖ The pathological hallmark of MS is the cerebral or spinal plaque, which consists of a discrete region of demyelination with relative preservation of axons, although spectroscopic and pathological studies suggest some axonal loss may be an integral part of the disease process.
- ❖ Gross examination of the brain in MS often reveals variable degrees of atrophy and ventricular dilatation.
- ❖ Plaques may be visible on the surface of the spinal cord on inspection.
- ❖ The cut surface of the brain reveals the plaques, which, when active, appear whitish yellow or pink, with somewhat indistinct borders.
- ❖ Older plaques appear translucent with a blue-gray discoloration and sharply demarcated margins.
- ❖ These plaques often have a hard or rubbery consistency.
- ❖ Individual lesions are generally small (1 to 2 cm), but may become confluent, generating large plaques.
- ❖ Plaques develop in a perivenular distribution and are seen most frequently in the periventricular white matter, brainstem, and spinal cord.
- ❖ However, large numbers of small plaques, often detected only by microscopy, are found in cortical regions affecting intracortical myelinated fibers.
- ❖ One of the earliest features of acute MS lesions is a disruption of the blood-brain barrier (BBB) as detected by MRI

❖ ETIOLOGY:

a) Autoimmunity

- Low levels of autoreactive T cells and B cells are present in normal individuals.

- Presumably they have escaped from clonal deletion during the process of immune development and are now tolerant of their antigens.
- Autoimmunity develops when these cells lose tolerance and a complex process of immune reactivity in target tissues begins.
- One potential way in which tolerance can be broken is by means of molecular mimicry between self-antigens and foreign antigens; for example, viral components.
- Several viral and bacterial peptides share structural similarities with important proteins of myelin, and a few of them are able to activate specific T-cell clones derived from patients with MS.
- Another way in which tolerance can be broken is by CNS infection, causing tissue damage and releasing antigens into the peripheral circulation, where they may encounter corresponding autoreactive T cells.
- Myelin basic protein (MBP) has long been considered one of the primary candidates for an autoimmune attack.
- T cells that respond to MBP are found in the peripheral blood in normal and in those with MS, possibly at higher levels in patients with MS with active disease.
- MBP, which accounts for 30% of the protein of myelin, can be an antigen for EAE, the primary animal model of MS.
- Recent clinical trials with altered peptide ligands of MBP support the potential pathogenic role of MBP-reactive T cells.

- Several other proteins characteristic of myelin are also candidates for an autoimmune attack.
- Proteolipid protein accounts for 50% of CNS myelin protein and is an integral membrane protein of the myelin leaflets.
- In the PNS, P0 protein fulfils this role.
- Myelin-associated glycoprotein, myelin oligodendrocyte glycoprotein, and cyclic nucleotide phosphodiesterase are proteins that account for a few percent of myelin.
- Myelin oligodendrocyte glycoprotein and cyclic nucleotide phosphodiesterase are not found in peripheral nerve myelin and are, therefore, of interest because MS is a disease affecting only central myelin.
- Although the possibility of autoimmunity as the causal mechanism for MS exists, the issue is not proven.
- The actual target antigen and the details of the immunopathological process are not yet fully understood.
- The evidence for MS being a dysimmune condition is more compelling; with alterations in immune cell repertoire and activation state both in blood andCSF of MS patients compared to others.

b) Infection

- A possible role for microbial infection in the causation of MS has been a matter of ongoing debate for decades.
- More recently, human herpesvirus-6 (HHV-6), Epstein-Barr virus (EBV), and *Chlamydia pneumoniae* have been the focus of interest as potential triggers for MS.
- Several studies of serum and CSF samples have yielded varying results. For example, one early study showed 47% of MS brains

were positive for HHV-6, and 80% showed elevation of antibodies in the serum.

- A more recent study found no HHV-6 DNA in any CSF sample, and the serum antibody titers were comparable to the general population.
- As has been stated before, the final word about viruses or other microbes and MS is pending.

❖ EPIDEMIOLOGY

a) Age of Onset

- Most studies agree that the mean and median age of onset inrelapsing forms of MS is age 29 to 32.
- The peak age of onset is approximately 5 years earlier for women than for men. Primary progressive MS has a mean age of onset of 35 to 39 years.

b) Sex Distribution

- Autoimmune diseases in general and MS in particular affect more women than men.
- In a summary of 30 incidence and prevalence studies, a cumulative ratio of female to male subjects was 1.77 to 1.00.

c) Geographical and Racial Distribution

- High-frequency areas of the world, with current prevalence of 30 per 100,000 or more, include all of Europe (including Russia), southern Canada, the northern United States, New Zealand, and the southeastern portion of Australia.
- Medium frequency areas with prevalence of 5-25 per 100,000 comprise most of Australia, the southern United States, the Mediterranean basin (other than Italy), the Asian parts of the former Soviet Union, parts of South America, and the white population of South Africa.
- Low-risk areas with prevalence of less than 5 per 100,000 include most of South America, Mexico, most of Asia, and all of Africa. One possible conclusion is that MS is a location-related illness, with a latitude gradient.

d) Genetics

- The frequency of familial occurrence of MS has varied from 3% to 23% in different studies.
- An overall risk in first degree relatives of 5% seems a reasonable estimate. The risk is highest for siblings and decreases progressively for children, aunts, uncles, and cousins.
- For genetic counseling purposes, the sibling risk is 3% to 5%, approximately 30 to 50 times the background risk for this same population. In some studies unaffected family members may have been found to have abnormalities on MRI, implying that the risk may be even higher.
- Several candidate genes for MS have been identified, including those coding for human leukocyte antigen (HLA), T-cell receptor, MBP, portions of the immunoglobulin chain, and mitochondrial genes.
- Three entire genomic scans for MS susceptibility genes have been reported, without an identifiable region of major interest beyond the HLA complex region of chromosome 6.
- The data argue for non- Mendelian polygenic inheritance.

❖ CLINICAL SYMPTOMS AND PHYSICAL FINDINGS

- Although the clinical syndrome of MS is classically described as a relapsing-remitting disorder that affects multiple white matter tracts within the CNS, with usual onset in young adults, the disorder displays marked clinical heterogeneity.
- This variability includes age of onset, mode of initial manifestation, frequency, severity and sequelae of relapses, extent of progression, and cumulative deficit over time.
- The varied clinical features reflect the multifocal areas of CNS (primarily myelin) destruction (MS plaques), although discrepancies occur between the extent of clinical and pathological findings.
- The high degree of variability and the difficulty in predicting the course and severity make MS one of the most puzzling of CNS diseases.
- The symptoms and signs of MS primarily reflect conduction block from large demyelinated segments or axonal damage as well as conduction delay through smaller demyelinated segments, which produce critical temporal dispersion.

1) Cognitive Impairment

- Data from formal neuropsychological studies indicates that cognitive involvement has been underreported in MS.
- Neuropsychological test results have shown that 34% to 65% of patients with MS have cognitive impairment.
- The most frequent abnormalities are with abstract conceptualization, recent memory, attention, and speed of information processing.
- Patients complain of memory loss or frustration.
- The abnormalities are usually not apparent during a routine office visit.
- The cognitive deficit of the MS patient is most obvious when he or she confronts multiple stimuli in a pressured environment.

2) ***Affective Disorders***

- Depression is the most common manifestationand is in part secondary to the burden of having to cope with a chronic, incurable disease.
- However, it is more prevalent in MS than in other chronic diseases, suggesting an organic component as well.

- The lifetime risk of major depression in patients with MS is up to 50%, compared with 12.9% in patients with chronic medical conditions in another study.

- Some data indicate a comorbid association, presumably genetic, between bipolar illness and MS. Suicide rates are higher in patients with MS than in the general population or when compared to patients with other chronic illnesses.
- Frontal or subcortical white matter disease may also be a contributory causative factor.
- Euphoria, formerly considered to be common in MS, is actually infrequent and is usually associated with moderate or severe cognitive impairment and greater disease burden on MRI.
- Patients may manifest a dysphoric state with swings from depression to elation.

3) ***Cranial Nerve Dysfunction***

i. Impairment of the Visual Pathways

- Optic neuritis (ON) is the most frequent type of involvement of the visual pathways, usually presenting as an acute or subacute unilateral syndrome characterized by pain in the eye accentuated

by ocular movements, which is followed by a variable degree of visual loss affecting mainly central vision.

- Recurrence is highly variable.
- Mapping of visual fields reveals a central or cecocentral scotoma (central scotoma involving the physiological blind spot).
- The lesion of the optic nerve is retrobulbar, and funduscopic examination is normal in the acute stage.
- Later the optic disc becomes pale as a result of axonal loss. This pallor predominates in the temporal segment of the disc (temporal pallor).
- After an attack of acute ON, 90% of patients regain normal vision, typically over a period of 2 to 6 months.
- Desaturation of bright colors, particularly red, is often reported by recovered patients; some also report a mild nonspecific dimming of vision in the affected eye.

- ***Uhthoff's phenomenon*** *refers to a decrease in visual acuity following an increase in body temperature. This can occur after exercise, a hot bath, or fever. This phenomenon, which reflects subclinical demyelination or preexistent injury to the optic nerve, may occur without a history of clinical involvement of the optic nerve. A similar phenomenon can occur at other sites of CNS damage with an increase in body temperature.The basis for this phenomenon is an alteration in conduction efficiency when body temperature rises such that subclinical conduction defects become clinically apparent.*

ii. Impairment of the Ocular Motor Pathways

- Impairment of individual ocular motor nerves is infrequent in MS.
- When present, the involved nerves are, in decreasing order of frequency, cranial nerves VI, III and, rarely, IV.
- More frequent findings are those that reflect lesions of vestibulo-ocular connections and internuclear connections.

Internuclear ophthalmoplegia*, defined as abnormal horizontal ocular movements with lost or impaired adduction and horizontal nystagmus of the abducting eye, is secondary to a lesion of the medial longitudinal fasciculus on the side of diminished adduction.*

iii. Impairment of Other Cranial Nerves

- Impairment of facial sensation, subjective or objective, is a relatively common finding in MS.
- The occurrence of trigeminal neuralgia in a young adult is frequently an early sign of MS.

- *Facial myokymia,* a fine undulating wavelike facial twitching, and hemifacial spasm can be caused by MS, but other causes of a focal brainstem lesion must be excluded.
- Unilateral facial paresis can occur, but taste sensation is almost never affected. In these syndromes, as with acute oculomotor palsy, the nerve is affected in its course within the brainstem, rather than peripherally.
- Vertigo is a reported symptom in 30% to 50% of patients with MS and is commonly associated with dysfunction of adjacent brainstem or cranial nerves.
- Resulting associated symptoms include hyperacusis or hypoacusis, facial numbness, and diplopia.
- Complete hearing loss, usually unilateral, is an infrequent complaint.
- Malfunction of the lower cranial nerves is usually of the upper motor neuron type (pseudobulbar syndrome) and is usually a rather late finding in MS.

4) Impairment of the Sensory Pathways

- Sensory manifestations are a frequent initial feature of MS and are present in almost every patient at some time during the course of disease.
- The sensory features can reflect spinothalamic, posterior column, or dorsal root entry zone lesions.
- The sensory symptoms are commonly described as numbness, tingling, pins and needles, tightness, coldness, itching, or swelling of limbs or trunk.
- Radicular pains, unilateral or bilateral, can be present, particularly in the low thoracic and abdominal regions, or a bandlike abdominal sensation may be described.
- The most frequent sensory abnormalities on clinical examination are varying degrees of impairment of vibration and joint position sense, decrease of pain and light touch in a distal distribution in the four extremities, and patchy areas of reduced pain and light touch perception in the limbs and trunk.

5) Impairment of the Motor Pathways

- Corticospinal tract dysfunction is common in MS.
- Paraparesis, or paraplegia, occurs more frequently than significant weakness in the upper extremities.
- With severe spasticity, extensor or flexor spasms of the legs and sometimes the trunk may be provoked by active or passive attempts to rise from a bed or wheelchair.

- The physical findings include spasticity, usually more marked in the legs than in the arms.
- The deep tendon reflexes are exaggerated, sustained clonus may be elicited, and extensor plantar responses are observed.
- All of these manifestations are commonly asymmetrical.

6) Impairment of Cerebellar Pathways

- Cerebellar pathway impairment results in gait imbalance, difficulty in performing coordinated actions with the arms, and slurred speech.
- Examination reveals the usual features of cerebellar dysfunction, such as dysmetria, decomposition of complex movements, and hypotonia, most often observed in the upper extremities.
- An intention tremor in the limbs and titubation of the head may be seen, Walking is impaired by ataxia.
- Ocular findings of nystagmus, ocular dysmetria, and frequent refixation saccades suggest cerebellar or cerebellovestibular connection dysfunction. Speech can be scanning or explosive in character.

7) Impairment of Bladder, Bowel, and SexualFunctions

- The extent of sphincter and sexual dysfunction often parallels the degree of motor impairment in the lower extremities.
- The most common complaint related to urinary bladder dysfunction is urgency, usually the result of uninhibited detrusor contraction, reflecting a suprasegmental lesion.

- Constipation is more common than fecal incontinence and is mainly due to decreased general mobility and the tendency of MS patients to restrict their fluid intake in a misguided attempt to decrease urinary urgency and incontinence. Almost all patients with paraplegia require special measures to maintain regular bowel movements.
- Sexual dysfunction, although frequently overlooked, occurs commonly in MS. Approximately 50% of patients become completely sexually inactive secondary to their disease, and an additional 20% become sexually less active.
- Men experience various degrees of erectile dysfunction, often with rapid loss of erection at attempted intercourse.
- Most women preserve their orgasmic capabilities, sometimes even in the presence of complete loss of bladder and bowel function.

CLINICAL FEATURES SUGGESTIVE OFMS	***CLINICAL FEATURES NOT SUGGESTIVE OF MS***
Onset between ages 15 and 50	Onset before age 10 or after age 60
Involvement of multiple areas of the CNS	involvement of the PNS
Optic neuritis	Hemianopsias
Lhermitte's sign	Rigidity, sustained dystonia
Internuclear ophthalmoplegia	Cortical deficits such as aphasia,apraxia,alexia, neglect
Fatigue	Deficit developing within minutes
Worsening with elevated body temperature	Early dementia

❖ DIAGNOSTIC CRITERIA

- More recently, McDonald and colleagues proposed new diagnostic criteria that include detailed guidelines for MRI and timing intervals to determine possible or definite MS.

❖ Paraclinical Evidence in MS Diagnosis:

- ***WHAT IS A POSITIVE MRI?***

Three out of four of the following:

• 1 gadolinium-enhancing brain or cord lesion ***or*** 9 T2 hyperintense brain and/or cord lesions if there is no gadolinium- enhancing lesion

• 1 or more brain infratentorial or cord lesions

• 1 or more juxtacortical lesions

• 3 or more periventricular lesions

Note: *Individual cord lesions can contribute along with individual brain lesions to reach required number of T2 lesions***.**

- ***WHAT PROVIDES MRI EVIDENCE OF DISSEMINATION IN TIME?***

A gadolinium-enhancing lesion detected in scan at least 3 months after onset of initial clinical event at a site different from initial event ***- or -***

A new T2 lesion detected in a scan done at any time compared to a reference scan done at least 30 days after initial clinical event

- ***WHAT IS POSITIVE CSF?***

  Oligoclonal IgG bands in CSF (and not serum) ***or*** elevated IgG index

- ***WHAT IS POSITIVE VEP?***

  Delayed but well-preserved waveform

❖ Differential Diagnosis in Multiple Sclerosis

INFLAMMATORY DISEASES
Granulomatous angiitis
Systemic lupus erythematosus
Sjögren's disease
Behçet's disease
Polyarteritis nodosa
Paraneoplastic encephalomyelopathies
Acute disseminated encephalomyelitis, postinfectious encephalomyelitis
INFECTIOUS DISEASES
Lyme neuroborreliosis
Human T-cell lymphotropic virus type 1 infection*
Human immunodeficiency virus infection
Progressive multifocal leukoencephalopathy*
Neurosyphilis*
GRANULOMATOUS DISEASES
Sarcoidosis
Wegener's granulomatosis
Lymphomatoid granulomatosis
DISEASES OF MYELIN
Metachromatic leukodystrophy (juvenile and adult)*
Adrenomyeloleukodystrophy*
MISCELLANEOUS
Spinocerebellar disorders*
Arnold-Chiari malformation
Vitamin B12 deficiency*
*Indicates disorders that are predominantly important to differentiate in the setting of progressive disease.

❖ Revised McDonald et al. (2005) Diagnostic Criteria for Multiple Sclerosis

CLINICAL (ATTACKS)	OBJECTIVE LESIONS	ADDITIONAL REQUIREMENTS TO MAKE DIAGNOSIS
2 or more	2 or more	None. Clinical evidence alone will suffice; additional evidence desirable but must be consistent with MS
2 or more	1 consistent with MS	Dissemination in space by MRI ***or*** 2 or more MRI lesions plus positive CSF ***or*** await further clinical attack implicating other site
1	2 or more	Dissemination in time by MRI ***or*** second clinical attack
1	1 consistent with MS	Dissemination in space by MRI ***or*** 2 or more MRI lesions plus positive CSF **AND** dissemination in time by MRI ***or*** second clinical attack
0 (progression from onset) **AND** 2 out of 3 of the following: Positive brain MRI (9 T2 lesions ***or*** 4 or more T2 lesions with positive VEP) Positive spinal cord MRI (2 or more focal T2 lesions) Positive CSF	1 or more	Disease progression for 1 year (retrospective or prospective)

❖ Effect of Exogenous Factors on the Course

- A disproportionately high number of relapses occur in patients with MS who have suffered recently from viral infections, and a high number of infections are followed by acute attacks.
- Increased interferon- g and TNF-a produced by cells of the immune system during viral infections may play a role in this increased relapse rate by increasing expression of major histocompatibility complex class II antigens and adhesion molecules on cells of the immune system and CNS, with a resultant increase in the number of activated T cells being attracted to the CNS.
- Controversy exists about a link between occurrence of stressful events and exacerbation of MS.
- Trauma appears not to be implicated in disease induction or relapse. Performance of neurological diagnostic procedures such as myelography and lumbar puncture has not been linked with

aggravation of the MS disease course, nor has administration of local or general anesthetics or surgery.

- Recent data do not establish a link between vaccination and disease exacerbations, and there are no convincing data to support withholding immunizations for example, for influenza or hepatitis.

Effect of Pregnancy on the Course

- MS is a disease that predominantly affects women and has a maximum incidence during childbearing years. The influence of pregnancy on MS has been repeatedly examined, with evidence that relapses are reduced during pregnancy and are more frequent than expected in the 3-month postpartum period
- There is general agreement that the overall prognosis is no different in women who have been pregnant, compared with those who have not.
- Studies of women with MS reveal no increase in stillbirths, ectopic pregnancies, or spontaneous abortions.
- These data would suggest that pregnancy has no ill effect on MS and that MS has no negative effect on the fetus or the course of pregnancy.

❖ PROGNOSIS

Although great individual variability exists with regard to disease prognosis, a variety of factors have been identified as possible prognostic indicators.

- *Sex:* MS appears to follow a more benign course in women than in men.
- *Age at onset:* The average age at onset of MS is 29 to

32 years. Onset at an early age is seemingly a favourable factor, whereas onset at a later age carries a less favourable prognosis. As previously stated, the pattern of disease varies in different age groups, with the relapsing-remitting form being more common in younger patients and the progressive form being more common in the older age group. Data are lacking as to whether prognosis differs as a function of age in patients with similar patterns of disease.

- *Initial disease course:* The relapsing form of the disease is associated with a better prognosis than progressive disease.
- *Initial complaints:* Among initial symptoms, impairment of sensory pathways or cranial nerve dysfunction, particularly ON, has been found in several studies to be a favourable prognostic feature, whereas pyramidal and particularly brainstem and cerebellar symptoms carry a poor prognosis.

❖ DIAGNOSTIC STUDIES

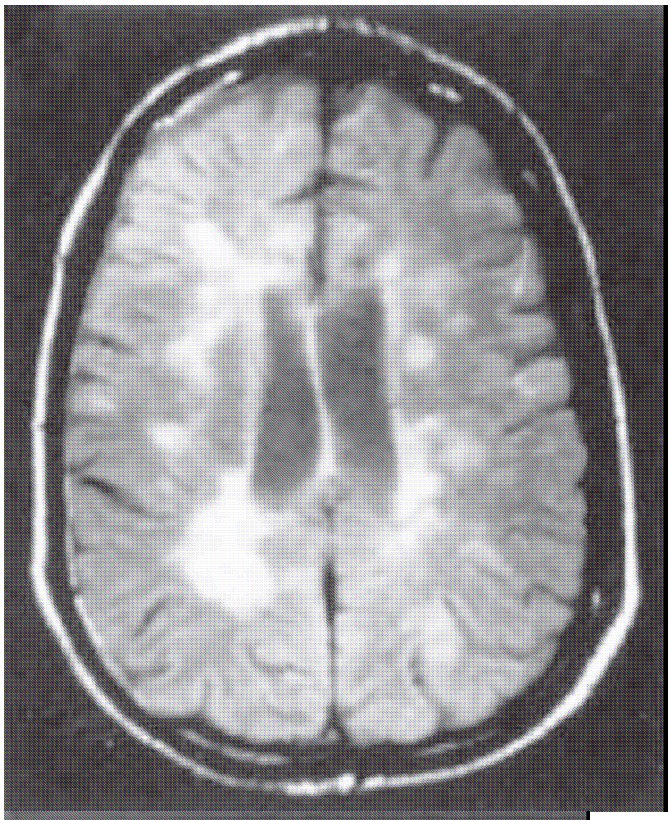
Although the diagnosis of MS remains clinical, a number of ancillary laboratory tests can aid in the diagnosis of MS.

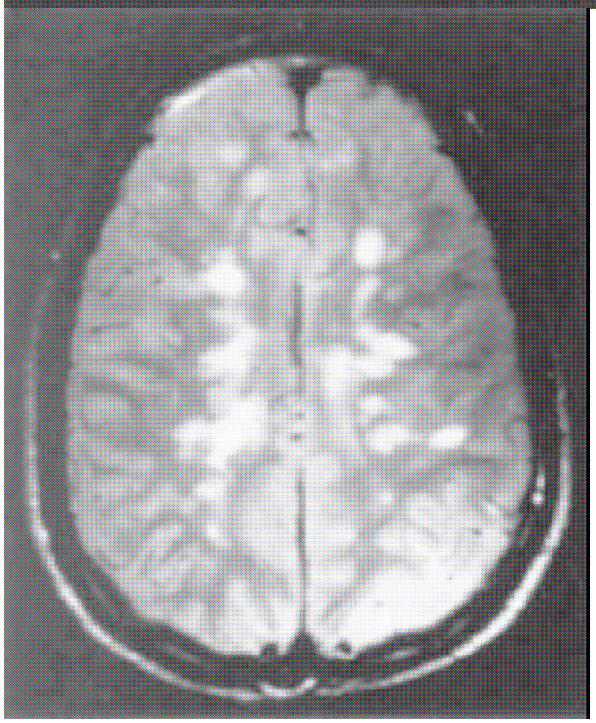
- **Neuroimaging**

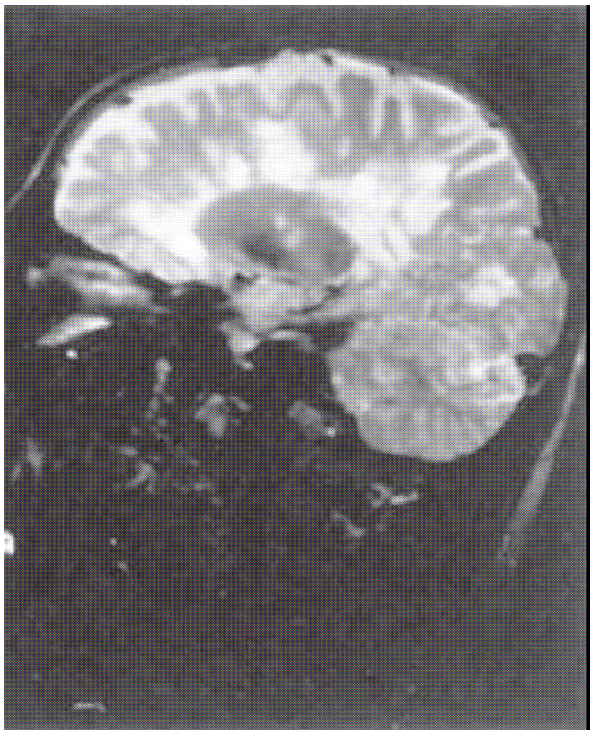
✓ ***Magnetic Resonance Imaging***

- MRI has significantly changed the diagnostic approach to MS and is now the modality of choice to augment clinical information.
- MS plaques are typicallyfound in the periventricular region, corpus callosum, centrum semiovale and, to a lesser extent, deep white matter structures and basal ganglia.

- Typical MS plaques often have an ovoid appearance and lesions arranged at right angles to the corpus callosum as if radiating from it (Dawson's fingers).
- The plaques appear hyperintenseon proton density and T2-weighted studies, whereas the plaques appear (if visible at all) hypointense on T1-weighted images.
- Such hypointense lesions on T1-weighted scans (black holes) are associated with axonal loss in addition to demyelination and indicate a poorer prognosis.







- **<u>Cerebrospinal Fluid Analysis</u>**
- CSF findings alone cannot make or exclude the diagnosis of MS, but they can be useful adjuncts to clinical criteria.
- The CSF is grossly normal in MS, being clear, colorless, and under normal pressure.
- Total leukocyte count is normal in two thirds of patients, exceeding 15 cells/mL in less than 5% of patients and only rarely exceeding 50 cells/mL (a finding that should raise suspicion of another etiology).
- The predominant cell type is the lymphocyte, the vast majority of which are T cells.
- CSF protein (or albumin) level is normal in the majority of patients with MS.
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- Albumin determinations are preferable because albumin is not synthesized in the CNS; thus this gives a better indication of BBB disruption than does total protein, some of which may be synthesized within the CNS (i.e., immunoglobulin).
- Albumin levels are elevated in 20% to 30% of patients, although less than 1% of
- **Evoked Potentials**
- EPs, the CNS electrical events generated by peripheral stimulation of a sensory organ, are useful in detecting a CNS abnormality of function that may be clinically inapparent.
- In the case of MS, detection of a subclinical lesion in a site remote from the region of clinical dysfunction supports a diagnosis of multifocal disease.
- The EPs also may help define the anatomical site of the lesion in tracts not easily visualized by imaging (i.e., optic nerves, dorsal columns).
- The three most frequently used EPs are somatosensory (SSEP), visual evoked response (VER), and brainstem auditory-evoked responses (BAER).
- Because of its higher sensitivity and its ability to provide anatomical information, MRI has largely eliminated the utility of EPs in the diagnosis of MS.
- SSEPs are abnormal in 65% to 80% of patients with MS, including approximately one half of patients with MS who do not have sensory signs or symptoms.

❖ TREATMENT AND MANAGEMENT

- In prior decades, many clinicians and patients adopted a nihilistic and pessimistic attitude about MS because effective treatment of this often progressive disease of young adults was unavailable.
- The advent of more effective symptomatic therapy and the widely publicized U.S. Food and Drug Administration (FDA) approval over the past 14 years of six agents capable of modifying the disease course have drastically changed that view.
- Many problems remain, particularly the treatment of progressive MS, yet there are clearly reasons for hope.

Treatment of MS should be directed toward these basic goals:

- Relief or modification of symptoms
- Shortening the duration or limiting the residual effects ofan acute relapse
- Reducing the frequency of relapses
- Preventing progression or slowing its pace
- Supporting family and patient, alleviating social and economic effects, and advocating for the disabled or handicapped.

- **Relief or Modification of Symptoms**

1) Spasticity

- Spasticity slows voluntary movement, impairs balance and gait, and may cause painful flexor or extensor spasms.
- Partial control is often possible, although recovery of motor power is rare.
- Baclofen is a g-aminobutyric acid agonist that can effectively relieve spasms and has modest effects in improving performance. Daily divided doses of 20 to 120 mg and occasionally more are

used. Too large a dose may produce drowsiness or hypotonicity sufficient to aggravate weakness, especially in those individuals who require a degree of spasticity to stand

- Tizanidine (Zanafl ex), a centrally active a2-noradrenergic agonist, may be used alone or in combination with baclofen because the mechanism of action is different. The medication should be gradually increased starting with 2 mg at bedtime.
- The Dantrolene sodium (Dantrium), an agent that acts within muscles on excitation-contraction coupling, is rarely used because of the risk of liver damage. If used, the medication must be titrated from 25 mg daily up to 100 mg three times a day.
- Botulinum toxin type A (Botox) also has been shown to be effective in selective cases.

2) Fatigue

- Fatigue occurs in as many as 78% of patients and interferes with daily activities.
- Fatigue must be separated from depression, medication side effects, and physical exhaustion from gait alterations.
- Amantadine (Symmetrel), 100 mg twice a day, has relatively few side effects and is well tolerated by most patients. Caution must be taken in patients with renal insufficiency or seizure disorders. Studies have found an efficacy rate of 40%.
- Modafinil (Provigil) is a wakefulness-promoting agent that is chemically and pharmacologically distinct from CNS stimulants, although the precise mechanism of action is unknown.

3) Depression

- Prevalence rates for depression in patients with MS range from 14% to 57%, as compared with 1.3% to 3.7% in the general population.
- The lifetime prevalence of depression in a group of patients with chronic medical disorders was 12.9%.
- The nature of a chronic debilitating neurological disorder contributes to depressive symptoms and coping problems.
- Patients taking multiple medications are prone to depression, and the side effect profile of the interferon-beta medications includes depression.
- Selective serotonin reuptake inhibitors are the medications of choice for depressive symptoms in patients with MS.
- In additionto the previously mentioned fluoxetine, any of the other medications in this class may be used.

4) Sexual Dysfunction

- Studies suggest that 45% to 74% of women with MS experience sexual dysfunction. These symptoms have been associated with depression, bowel dysfunction, fatigue, spasticity, and pelvic floor weakness.
- There was no association between duration of disease, type of disease, recent exacerbations, or disability scores.
- Erectile dysfunction in men is common, especially in patients with spinal cord involvement. Adverse effects of medication or psychological issues may also be associated with sexual dysfunction.

- Sildenafil (Viagra) and similar medications have supplanted older approaches to erectile dysfunction in men, which included intracavernous papaverine, prostaglandin E, phentolamine, vacuum devices, and penile prostheses. Sildenafil in doses of 25 to 100 mg 1 hour before sexual intercourse is used with minimal side effects, which include headache, flushing, dyspepsia, and musculoskeletal pain. Reports suggest caution in patients with cardiovascular disease.

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5) Paroxysmal Symptoms

- Paroxysmal symptoms in MS consist of brief, almost stereotypical, events occurring frequently and often triggered by movement or sensory stimuli. They are likely caused by ephaptic transmission of nerve impulses at sites of previous disease activity.
- These symptoms include, but are not limited to, trigeminal neuralgia, pain, paresthesia, weakness, tonic seizures, dysarthria and ataxia, pruritus, diplopia, akinesia, hemifacial spasm, and dystonia.
- Anticonvulsants have been used in their usual or lower doses with some benefit. Benzodiazepines also have been effective in some patients. Baclofen, acetazolamide (Diamox), ibuprofen, and bromocriptine have been cited as potentially beneficial with these paroxysmal symptoms.
- **Treatment of Acute Attacks**
- Acute attacks are typically treated with corticosteroids.
- Indications for treatment of a relapse include functionally disabling symptoms with objective evidence of neurological impairment.
- Thus, mild sensory attacks are typically not treated.

- treatment with short courses of intravenous methylprednisolone, 500 to 1000 mg daily for 3 to 7 days, with or without a short prednisone taper, has commonly been used.
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- **Disease-modifying Treatments**

As of April 2013, eight disease-modifying treatments have been approved by regulatory agencies of different countries. The approved drugs are ***interferon beta-1a, interferon beta-1b, glatiramer acetate, mitoxantrone, natalizumab, fingolimod, teriflunomide*** and ***dimethyl fumarate***

- The first medication approved by the FDA for use in MS was recombinant interferon beta-1b ***(Betaseron***), which was shown in a 1993 double-blind, placebo-controlled trial of 372 patients to decrease the frequency of relapses by 34% after 2 years in relapsing-remitting patients receiving 8 mIU every other day.
- In treated patients, the MRI T2 lesion burden increased 3.6% over 5 years, compared with 30.2% in the placebo group.
- No significant change in disease progression occurred over 5 years. Interferon beta-1b is administered subcutaneously every other day by self-injection. Side effects include
- influenza-like symptoms, which usually diminish over weeks to months, depression, and reactions at the injection site. Elevated liver enzymes, leukopenia, and anemia were seen, and blood monitoring is recommended every 3 months.
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Avonex interferon beta-1a **:W**eekly intramuscular injections of 6 million U (30 mg)

Rebif: Subcutaneous interferon beta-a 22 mg, or 44 mg of interferon beta-1a three times a week.

glatiramer acetate (Copaxone), 20 mg SC daily

❖ **OTHER INFLAMMATORY DEMYELINATING DISEASES OF THE**

1. Devic's Disease (Neuromyelitis Optica)

- A combination of bilateral optic neuropathy and myelopathy characterize this condition, which many authorities now classify as a separate entity rather than a variant of MS.
- The myelopathy tends to be more severe than typically occurs with MS, with less likelihood of recovery.
- The neuropathological features at autopsy are those of a much more severe necrotic lesion of the cord rather than incomplete demyelination.
- In some patients the optic neuropathy and the myelopathy occur at the same time; in others one or the other component is delayed. Recent findings of an antibody to the aquaporin-4 water channel in a high frequency of patients with the clinical characteristics of Devic's disease and low frequency in typical MS, suggests that these may be different conditions.

2. Acute and Subacute Transverse Myelitis

- *Acute and subacute transverse myelitis* is defined as the development of isolated spinal cord dysfunction over hours or days in patients in whom no evidence exists of a compressive lesion.
- In the combined experience of several series reviewing complete transverse myelitis, 37% of patients reported a preceding febrile illness. The initial symptoms are paresthesias, back pain, or leg weakness; 37% of patients had the maximal deficit within 1 day, 45% in 1 to 10 days, and 18% in more than 10 days.
- Outcome was rated as good in 42%, fair in 38%, and poor in 20%. The prognosis may be worse in the rapid-onset group of patients.
- Only approximately 7% of patients develop MS by clinical criteria.
- Whether these cases represent a homogeneous entity remains highly questionable, particularly because the ages of reported cases range from 4 to 83 years.
- In addition, acute transverse myelitis is known to occur on a background of systemic vasculitis, such as that seen in SLE and that associated with heroin abuse.
- One must distinguish complete transverse myelitis from the partial or incomplete syndromes that more frequently predict evolution to MS in 50% to 90% of patients. treatment with short courses of intravenous methylprednisolone, 500 to 1000 mg daily for 3 to 7

days, with or without a short prednisone taper, has commonly been used

3. Optic Neuritis

- The clinical features of ON are described in the section on MS. In ON associated with MS, the majority of clinical episodes are unilateral, although VERs also may indicate involvement of the contralateral eye.
- Simultaneous bilateral ON is rare in MS and somewhat more frequent in Devic's disease.
- The estimated incidence of subsequent development of MS following an initial episode of ON varies widely among different series (from less than 20% to more than 70%).
- The issue remains whether some cases of isolated ON do represent formes frustes of ADEM. In this regard, cases of ON occurring after childhood exanthemas would represent the best example of parainfectious ON. Cases have been reported following measles, rubella, mumps, and varicella.
- The young age of the patients further suggests that these events are not the initial manifestations of MS. The prognosis for recovery of vision is good in most cases, perhaps less so in postvaricella cases. treatment with short courses of intravenous methylprednisolone, 500 to 1000 mg daily for 3 to 7 days, with or without a short prednisone taper, has commonly been used

Peripheral neuropathy (PN)

(Dr. Ibrahim Alahmar)

❖ **Peripheral neuropathy (PN)** is damage or disease affecting nerves, which may impair sensation, movement, gland or organ function, or other aspects of health, depending on the type of nerve affected.

- In conventional medical usage, the word ***neuropathy*** (neuro-, "nervous system" and -pathy, "disease of") without modifier usually means peripheral neuropathy.
- **Peripheral neuropathy** may affect Motor nerves (that control muscles), sensory nerves, or autonomic nerves (that control automatic functions such as heart rate, body temperature and breathing).
- More than one type of nerve may be affected at the same time.
- **causes** :
  - ***inherited*** (present from birth).
  - ***systemic*** diseases (such as diabetes or leprosy)
  - ***vitamin deficiency***
  - ***medication*** (e.g., chemotherapy)
  - ***traumatic injury***
  - excessive alcohol consumption
  - ***immune*** system disease
  - ***Infection***

❖ **Classification**:

-Peripheral neuropathies may be classified according to:

1- The *type of nerve* predominantly involved (motor, sensory, autonomic)

Neuronopathies and Neuropathies with Predominantly Motor Manifestations

1. **Multifocal motor neuropathy***
2. **Guillain-Barré syndrome**
3. **Acute motor axonal neuropathy***
4. **Porphyric neuropathy**
5. **Chronic infl ammatory polyradiculoneuropathy**
6. **Neuropathy with osteosclerotic myeloma**
7. **Diabetic lumbar radiculoplexopathy**
8. **Hereditary motor sensory neuropathies (Charcot-Marie-Tooth disease)**
9. **Lead intoxication**

*Pure motor syndromes with normal sensory nerve action potentials

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2- The ***number and distribution*** of nerves affected (mononeuropathy, mononeuritis multiplex or polyneuropathy).

- Neuropathy affecting just **one** nerve is called ***"mononeuropathy"***
- Neuropathy involving **multiple nerves** in roughly the same areas on both sides of the body is called "symmetrical polyneuropathy" or simply ***"polyneuropathy"***
- When **two or more** (typically just a few, but sometimes many) separate nerves in disparate areas of the body are affected it is called ***"mononeuritis multiplex" "multifocal mononeuropathy***" or ***"multiple mononeuropathy***.

❖ **Causes of Multiple Mononeuropathies:-**

- Axonal injury
- Vasculitis (systemic, nonsystemic)
- Diabetes mellitus
- Sarcoidosis
- Hansen's disease (leprosy)
- Human immunodeficiency virus 1 infection
- Demyelination/conduction block
- Multifocal acquired demyelinating sensory and motor neuropathy
- Multifocal motor neuropathy
- Multiple compression neuropathies (hypothyroidism, diabetes)
- Hereditary neuropathy with liability to pressure palsies

3- The ***underlying cause***:

- Peripheral neuropathies are common neurological problems caused by disordered function and structure of peripheral motor, sensory, and autonomic nerves.

- The causes of neuropathies are disparate and their clinical presentations highly variable.
- ***The main causes of neuropathy are entrapment, diabetes, and other systemic diseases; inherited disorders; infl amatory demyelinating, ischemic, and paraneoplastic conditions; defi ciency states; infections; and toxins***.
- A logical systematic diagnostic approach to peripheral neuropathies consists of a (1) careful history, (2) detailed physical and neurological examination, and (3) electrophysiological studies, which not only confirm the presence of a peripheral nerve disorder but also shorten the list of diagnostic possibilities.
- The process affecting the nerves; e.g., inflammation (neuritis), compression (compression neuropathy), chemotherapy (chemotherapy-induced peripheral neuropathy). Where the cause is unknown it is described as idiopathic neuropathy.

- **Onset of Peripheral neuropathy** may be ***chronic*** (a long-term condition where symptoms begin subtly and progress slowly) or ***acute*** (sudden onset, rapid progress and slow resolution). Acute neuropathies demand urgent diagnosis.

❖ **Clinical pictures:**

- Neuropathy may cause painful cramps, fasciculations (fine muscle twitching), muscle loss, bone degeneration, and changes in the skin, hair, and nails.

- Additionally, ***motor neuropathy*** may cause impaired balance and coordination or, most commonly, muscle weakness; ***sensory neuropathy*** may cause numbness to touch and vibration, reduced position sense causing poorer coordination and balance, reduced sensitivity to temperature change and pain, spontaneous tingling or burning pain, or skin allodynia (severe pain from normally nonpainful stimuli, such as light touch); and ***autonomic neuropathy*** may produce diverse symptoms, depending on the affected glands and organs, but common symptoms are poor bladder control, abnormal blood pressure or heart rate, and reduced ability to sweat normally.

❖ **Classification:**

1-Mononeuropathy

- ***Definition:*** is a type of neuropathy that only affects a single nerve.
- It is diagnostically useful to distinguish it from polyneuropathy because the limitation in scope makes it more likely that the cause is a localized trauma or infection.
- The most common ***cause*** of mononeuropathy is physical compression of the nerve, known as compression neuropathy. Carpal tunnel syndrome and axillary nerve palsy are examples of this.
- The "pins-and-needles" sensation of one's "foot falling asleep" (paresthesia) is caused by a compression mononeuropathy, which can be resolved merely by moving around and adjusting to a more appropriate position.
- Direct injury to a nerve, interruption of its blood supply (ischemia), or inflammation can also cause mononeuropathy.

2-Mononeuritis multiplex

- ***Definition:*** (occasionally termed ***polyneuritis multiplex***) is simultaneous or sequential involvement of individual noncontiguous nerve trunks, either partially or completely, evolving over days to years and typically presenting with acute or subacute loss of sensory and motor function of individual nerves.
- ***Clinical picture:*** The pattern of involvement is ***asymmetric***; however, as the disease progresses deficit(s) becomes more confluent and symmetrical, making it difficult to differentiate from polyneuropathy.
- Therefore, attention to the pattern of early symptoms is important.
- Mononeuritis multiplex may also cause ***pain,*** which is characterized as deep, aching pain that is worse at night and frequently in the lower back, hip, or leg.
- In people with diabetes mellitus, mononeuritis multiplex is typically encountered as acute, unilateral, severe thigh pain followed by anterior muscle weakness and loss of knee reflex.
- Electrodiagnostic studies will show multifocal sensory motor axonal neuropathy.
- **Causes:** It is caused by, or associated with, several medical conditions:

  - diabetes mellitus

- vasculitides: polyarteritis nodosa, Wegener's granulomatosis, and Churg–Strauss syndrome

- immune-mediated diseases like rheumatoid arthritis, lupus erythematosus (SLE)

- infections: leprosy, lyme disease, HIV

- sarcoidosis, amyloidosis

- cryoglobulinemia

- chemical agents, including trichloroethylene and dapsone

- rarely, the sting of certain jellyfish, such as the sea nettle

3-Polyneuropathy

- **Definition:** is a pattern of nerve damage which is quite different from mononeuropathy, often more serious and affecting more areas of the body.
- The term "peripheral neuropathy" is sometimes used loosely to refer to polyneuropathy.
- In cases of polyneuropathy, many nerve cells in various parts of the body are affected, without regard to the nerve through which they pass; not all nerve cells are affected in any particular case.
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- In distal axonopathy, one common pattern is that the cell bodies of neurons remain intact, but the axons are affected in proportion to their length.
- Diabetic neuropathy is the most common cause of this pattern.
- In demyelinating polyneuropathies, the myelin sheath around axons is damaged, which affects the ability of the axons to conduct electrical impulses.
- The third and least common pattern affects the cell bodies of neurones directly.
- This usually picks out either the motor neurones (known as motor neurone disease) or the sensory neurones (known as *sensory neuronopathy* or *dorsal root ganglionopathy*).
- The effect of this is to cause symptoms in more than one part of the body, often on left and right sides symmetrically.
- As for any neuropathy, the chief symptoms include weakness or clumsiness of movement (motor); unusual or unpleasant

sensations such as tingling or burning; reduction in the ability to feel texture, temperature, etc.; and impaired balance when standing or walking (sensory).

- In many polyneuropathies, these symptoms occur first and most severely in the feet.
- Autonomic symptoms may also occur, such as dizziness on standing up, erectile dysfunction, and difficulty controlling urination.
- Polyneuropathies are usually caused by processes that affect the body as a whole.
- Diabetes and impaired glucose tolerance are the most common causes.
- Other causes relate to the particular type of polyneuropathy, and there are many different causes of each type, including inflammatory diseases such as lyme disease, vitamin deficiencies, blood disorders, and toxins (including alcohol and certain prescribed drugs).
- Most types of polyneuropathy progress fairly slowly, over months or years, but rapidly progressive polyneuropathy also occurs.
- It is important to recognize that glucose levels in the blood can spike to nerve-damaging levels after eating even though fasting blood sugar levels and average blood glucose levels can still remain below normal levels (currently typically considered below 100 mg/dL for fasting blood plasma and 6.0% for HGBA1c, the test commonly used to measure average blood glucose levels over an extended period).
- Studies have shown that many of the cases of peripheral small fiber neuropathy with typical symptoms of tingling, pain, and loss of sensation in the feet and hands are due to glucose intolerance before a diagnosis of diabetes or pre-diabetes. Such damage is often reversible, particularly in the early stages, with diet, exercise, and weight loss.
- The treatment of polyneuropathies is aimed firstly at eliminating or controlling the cause, secondly at maintaining muscle strength and physical function, and thirdly at controlling symptoms such as neuropathic pain.

❖ **Autonomic neuropathy**

- **Autonomic neuropathy** is a form of polyneuropathy which affects the non-voluntary, non-sensory nervous system (i.e., the autonomic

nervous system), affecting mostly the internal organs such as the bladder muscles, the cardiovascular system, the digestive tract, and the genital organs.

- These nerves are not under a person's conscious control and function automatically.
- Autonomic nerve fibers form large collections in the thorax, abdomen, and pelvis outside the spinal cord. However, they have connections with the spinal cord and ultimately the brain.
- Most commonly autonomic neuropathy is seen in persons with long-standing diabetes mellitus type 1 and 2.
- In most but not all cases, autonomic neuropathy occurs alongside other forms of neuropathy, such as sensory neuropathy.

Neuropathies with Autonomic Nervous System Involvement

ACUTE

- Acute panautonomic neuropathy (idiopathic, paraneoplastic)
- Guillain-Barré syndrome
- Porphyria
- Toxic: vincristine

CHRONIC

- Diabetes mellitus
- Amyloid neuropathy (familial and primary)
- Paraneoplastic sensory neuropathy (malignant infl amatory sensory polyganglionopathy)
- Human immunodeficiency virus-related autonomic neuropathy
- Hereditary sensory and autonomic neuropathy

- Autonomic neuropathy is one cause of malfunction of the autonomic nervous system but not the only one; some conditions affecting the brain or spinal cord can also cause autonomic dysfunction, such as multiple system atrophy, and therefore cause similar symptoms to autonomic neuropathy.

The signs and symptoms of autonomic neuropathy include the following:

- Urinary bladder conditions: bladder incontinence or urine retention
- Gastrointestinal tract: dysphagia, abdominal pain, nausea, vomiting, malabsorption, fecal incontinence, gastroparesis, diarrhoea, constipation
- Cardiovascular system: disturbances of heart rate (tachycardia, bradycardia), orthostatic hypotension, inadequate increase of heart rate on exertion
- Respiratory system: impairments in the signals associated with regulation of breathing and gas exchange (central sleep apnea, hypopnea, bradypnea).[6]
- Other areas: hypoglycemia unawareness, genital impotence, sweat disturbances

Charcot-Marie-Tooth Disease (Hereditary Motor and Sensory Neuropathy)

- Charcot and Marie in Paris, and Tooth in London first described the syndrome of peroneal muscular atrophy, or CMT disease, in the second half of the nineteenth century.
- CMT disease is the most common inherited neuropathy, with an estimated prevalence of 1 in 2500 in the United States.
- Clinical studies combined with electrophysiological and sural nerve biopsy investigations of a large number of families with peroneal muscular atrophy has allowed a separation into two main groups
    - **The Demyelinating Form Or CMT1**, (formerly hereditary motor and sensory neuropathy [HMSN] type I) in which there is marked reduction in motor NCVs and nerve biopsy findings of demyelination and onion bulb formation; and
    - **The Axonal Form Of CMT Disease Or CMT2** (formerly HMSNtype II), in which motor NCVs are normal or near normal and nerve biopsy reveals axonal loss without demyelination.
- The peroneal muscular atrophy phenotype without sensory involvement on either clinical or electrophysiological examination has been classified as hereditary distal spinal muscular atrophy.
- A more severe form of demyelinating neuropathy with onset occurring in early childhood is referred to as *Dejerine-Sottas disease*.
- Both CMT1 and CMT2 display autosomal dominant inheritance.
- A minority of cases occur sporadically or in siblings only and have therefore been attributed to autosomal recessive inheritance or to de novo gene mutations. Because a great variability in clinical expression exists among affected kin
- In the dominant disorders, a recessive inheritance can only be accepted if the clinical and electrophysiological examinations of both parents have proved to be normal; even when the cause is non parental most of these patients phenotypically resemble CMT1. For any of these groups, an ever-increasing number of genetic subtypes have been described.

- ***Charcot-Marie-Tooth Disease 1***

- In CMT1, symptoms often begin during the first or second decade of life. Slowly progressive weakness, muscular wasting, and

sensory impairment predominantly involving the distal legs characterize it.

- Foot deformities and difficulties in running or walking resulting from symmetrical weakness and wasting in the intrinsic foot, peroneal, and anterior tibial muscles are often present. In two thirds of the patients the upper limbs are involved later in life.
- Inspection reveals pes cavus and hammer toes in nearly three quarters of adult patients; mild kyphosis in approximately a tenth; and palpably enlarged, hypertrophic peripheral nerves in a quarter.
- The foot deformities occur because of long-term muscular weakness and imbalance between the intrinsic extensor and long extensor muscles of the feet and toes (a similar process causes clawing of the fingers in more advanced cases).
- Absent ankle reflexes are universal and frequently associated with absent or reduced knee and upper limb reflexes.
- Some degree of distal sensory impairment (diminished vibration sense and light touch in the feet and hands) is usually discovered by examination, but rarely gives rise to symptoms.
- Occasionally, patients have an essential or postural upper limb tremor. Such cases have been referred to as *Roussy-Lévy syndrome*, but current evidence suggests that this is not a separate clinical or genetic entity. Motor nerve conduction studies show uniform slowing by more than 25% of the lower limits of normal in all nerves.
- Motor conduction of upper limb nerves proves more useful than studies of lower extremity nerves because distal denervation in the feet is often severe and virtually complete.
- A conduction velocity below 38 m per second in the forearm segment of the median nerve is proposed as a cut off value to distinguish between CMT disease types 1 and 2.
- Although this cut off is useful, it can be misleading if applied too rigidly. Sensory conductions are similarly abnormal.
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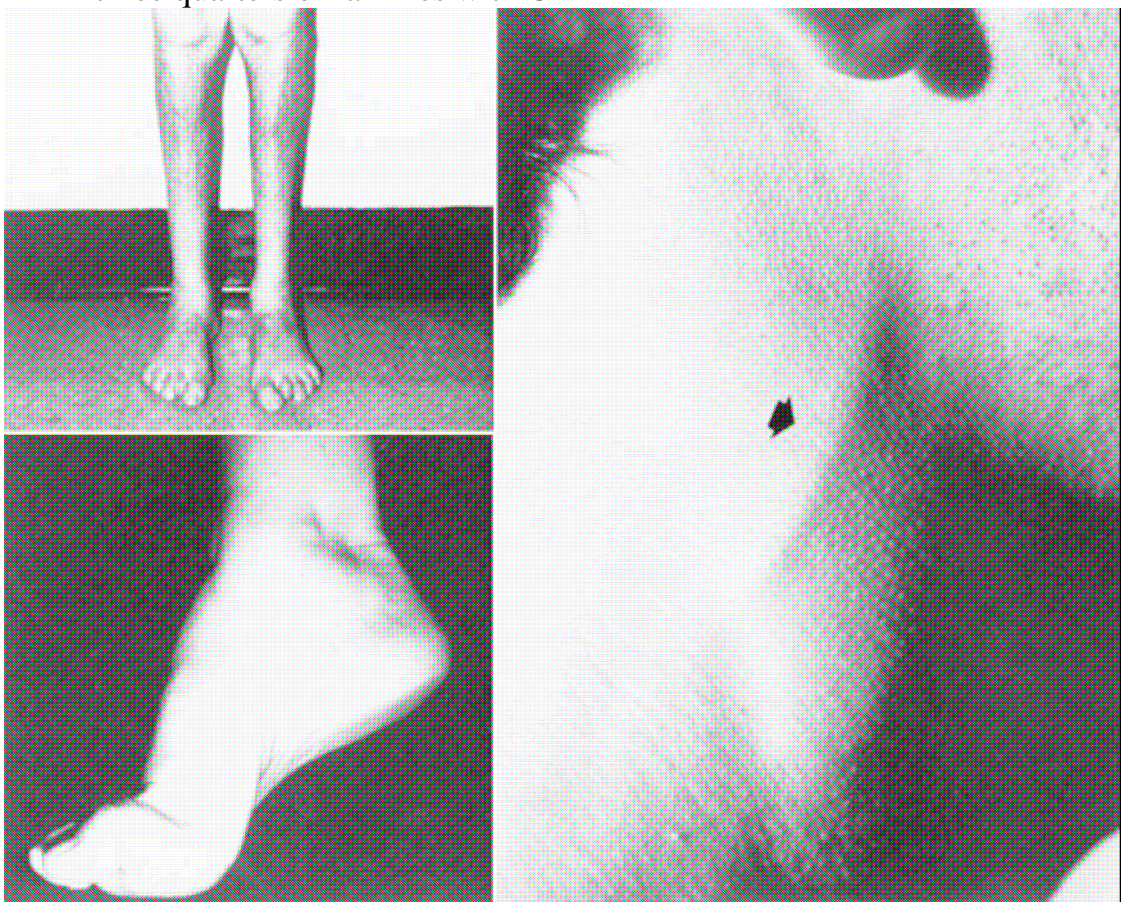
- SNAPs are usually absent with surface recordings.
- Routine hematological and biochemical studies are normal. CSF is also normal, which helps differentiate the condition from chronic inflammatory demyelinating poly neuropathy, in which the CSF protein is usually elevated.
- Sural nerve biopsy typically shows the changes of a hypertrophic neuropathy characterized by onion bulb formation, increased frequency of fibers with demyelinated and remyelinated segments,

an increase in endoneurial area, and loss of large myelinated fibers .

- Gene mutations, predominantly affecting genes for myelin and Schwann cell proteins, have been recognized that account for about three quarters of families with CMT1



Leg atrophy, pes cavus, and enlarged great auricular nerve (*arrow*) areevident in a patient with Charcot-Marie-Tooth type 1 disease

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❖ ***Treatment and Management***

- The rates of progression of CMT1 and CMT2 are slow, disability occurs relatively late, and life span may be normal.
- Management is mainly symptomatic.
- Patients should be instructed in proper foot care and advised to wear broad, well-fitting shoes.
- Insoles may be used to distribute body weight more evenly in patients with a foot deformity.
- Ankle-foot braces or orthopaedic procedures are indicated to correct for severe foot drop.

- Patients should be warned to avoid neurotoxic drugs because of greater susceptibility to agents such as vincristine.
- Issues like genetic counselling, family planning, prenatal diagnosis, and psychological concerns must be carefully approached, preferably by a multidisciplinary team, including a genetic counsellor.

❖ ***Phytanic Acid Storage Disease (Refsum's Disease)***

- Refsum's disease, heredopathia atactica polyneuritiformis, is a rare autosomal recessive disorder of phytanic acid metabolism.
- The gene defect has been localized to chromosome 10 and encodes the peroxisomal enzyme phytanoyl-CoA-hydroxylase.
- The defect in the enzyme that initiates the alpha-oxidation pathway of b-methyl substituted fatty acids leads to phytanic acid accumulation in serum and tissues.
- Phytanic acid is derived exclusively from dietary sources, mainly chlorophyll, dairy products, meats, and fish oils. Clinical onset spans from childhood to the third decade of life.
- The cardinal manifestations include pigmentary retinal degeneration, with night blindness or visual field constriction, chronic hypertrophic neuropathy, ataxia, and other cerebellar signs such as nystagmus and intention tremor.
- Initially, the neuropathy affects the lower limbs with distal leg atrophy, weakness, areflexia, large-fiber sensory impairment, and sometimes palpably enlarged nerves.
- Weakness becomes generalized later in the illness. In addition to pes cavus, overriding toes caused by symmetrically short fourth metatarsals are a helpful sign for Refsum's disease.
- Progressive sensorineural hearing loss, anosmia, cardiomyopathy, and ichthyosis are common.
- The course may be either progressive or fluctuating with exacerbations and remissions. Exacerbations are often precipitated by fasting, which mobilizes phytanic acid from endogenous fat stores.
- Motor conduction velocities are markedly slowed, and SNAPs are reduced or absent.
- CSF protein is increased in the range of 100 to 700 mg/dL. Sural nerve biopsy reveals a hypertrophic neuropathy with prominent onion bulb formation.
- The diagnosis is confirmed by elevated serum levels of phytanic acid.

- Chronic dietary treatment, by restricting the exogenous sources of phytanic acid (<10 mg/day) and its precursor phytol, results in reduction of serum phytanic acid levels and clinical improvement.
- The diet should provide sufficient calories to avoid weight loss.
- Plasma exchange has been used to lower toxic serum phytanic acid levels more rapidly in critically ill patients.

❖ ***Acute Infl ammatory Demyelinating Polyradiculoneuropathy (Guillain-Barré Syndrome)***

- In 1916, Guillain, Barré, and Strohl emphasized the main clinical features of GBS: motor weakness, areflexia, paresthesias with minor sensory loss, and increased protein in CSF without pleocytosis (albuminocytological dissociation).
- The frequent finding of motor conduction block and reduced NCVs provided further electrophysiological confirmation of the widespread demyelination.

- ***Diagnostic Criteria for Guillain-Barré Syndrome***
- **Features required for diagnosis**

1. Progressive ascending proximal weakness of both legs and arms
2. A reflexia

- **Clinical features supportive of diagnosis**

1. Progression over days to 4 wk
2. Relative symmetry of signs
3. Mild sensory symptoms or signs
4. Cranial nerve involvement (bifacial palsies)
5. Recovery beginning 2-4 wk after progression ceases
6. Autonomic dysfunction
7. Absence of fever at onset

- **Laboratory features supportive of diagnosis**

1. Elevated cerebrospinal fl uid protein with < 10 cells/mL
2. Electrodiagnostic features of nerve conduction slowing or block

- ***Classification of Guillain-Barré Syndrome (GBS) Subtypes***

1. Acute inflammatory demyelinating polyradiculoneuropathy
2. Acute motor axonal neuropathy
3. Acute motor sensory axonal neuropathy
4. Miller-Fisher syndrome
5. Acute pandysautonomia
6. Sensory GBS

❖ ***Clinical Features***

- The classical form of GBS is a non-seasonal illness that affects persons of all ages, but males are more often affected than females (1.5:1).
- With the virtual eradication of acute poliomyelitis, GBS has become the leading cause of acute paralytic disease in Western countries.
- The mean annual incidence is 1.8 per 100,000 population and has remained stable over the past three decades.
- Incidence rates increase with age from 0.8 in those younger than 18 years to 3.2 for those 60 years and older.
- Approximately two thirds of patients report a preceding event, most frequently an upper respiratory or gastrointestinal infection, surgery, or immunization 1 to 4 weeks before the onset of neurological symptoms. The agent responsible for the prodromal illness often

Antecedent Events of Guillain-Barré Syndrome*

ANTECEDENT EVENT	PERCENTAG
Respiratory illness	58
Gastrointestinal illness	22
Respiratory and gastrointestinal illness	10
Surgery	5
Vaccination	3
Other	2
SEROLOGICAL EVIDENCE OF SPECIFIC INFECTIOUS AGENTS	
Campylobacter jejuni	26
Cytomegalovirus	15
Epstein-Barr virus	8
Mycoplasma pneumoniae	10

- Patients with classic GBS may initially present with weakness, with or without paresthetic sensory symptoms
- .The fairly symmetrical weakness of the lower limbs ascends proximally over hours to several days and may subsequently involve arm, facial, and oropharyngeal muscles, and, in severe cases, respiratory muscles.
- Its severity varies from mild, in which patients are still capable of walking unassisted, to a nearly total quadriplegia.
- Hyporeflexia or areflexia are the invariable features of GBS but may be absent early in the course of the disease.

- By definition, progression of the clinical process ends by 1 to 4 weeks into the illness.
- Cranial nerve involvement has occurred in 45% to 75% of cases in different series.
- Facial paresis, usually bilateral, is found in at least in one half of patients. The proportion of patients developing respiratory failure and requiring assisted ventilation seems to increase with age and ranges from 12% in epidemiological series to 30% in hospital-based series.
- Sensory loss is not a prominent feature and is frequently limited to the distal impairment of vibration sense.
- Moderate to severe pain occurs in 85% of patients on admission to the hospital.
- Interscapular or low back pain with radiation into the legs is most common, sometimes raising concern about the possibility of an epidural hematoma or abscess.
- Dysesthetic pain described as burning or tingling of the limbs is present in approximately one half of patients.
- Unusual clinical variants with restricted patterns of weakness may cause diagnostic difficulty. Isolated weakness of the face, oropharynx, neck, and arms without involving the legs is a distinctive feature of the pharyngeal-cervical-brachial variant.
- Most of the clinically significant autonomic dysfunction occurs within the first 2 to 4 weeks of the illness, the peak period of paralysis. Its varied and complex manifestations may be related to either increased or decreased sympathetic parasympathetic activity, resulting in orthostatic hypotension, urinary retention, gastrointestinal atony, iridoplegia, episodic or sustained hypertension, sinus tachycardia, tachyarrhythmias, anhidrosis or episodic diaphoresis, and acral vasoconstriction.
- Excessive vagal activity accounts for sudden episodes of bradycardia, heart block, and asystole.
- These “vagal spells” may occur spontaneously or may be triggered by tracheal suctioning or similar stimuli.
- Serious cardiac arrhythmias with hemodynamic instability tend to be more frequent in patients with severe quadriparesis and respiratory failure. Autonomic dysfunction can result in electrocardiographical changes including T-wave abnormalities, ST-segment depression, QRS widening, QT prolongation, and various forms of heart block.

Treatment

- Patients with rapidly worsening acute GBS should be observed in the hospital until the maximum extent of progression has been established.
- The reduction in mortality to less than 5% reflects improvements in modern critical care.
- Supportive care in intensive care units and the prevention of complications, of which respiratory failure and autonomic dysfunction are the most important, provide the best chance for a favorable outcome.
- Respiratory and bulbar function, the ability to handle secretions, heart rate, and blood pressure, should be closely monitored during the progressive phase. Respiratory failure requiring mechanical ventilation develops in up to 30%of patients with GBS.
- Subcutaneous heparin or low-molecular-weight heparin together with calf compression devices should be ordered routinely in immobilized patients to lower the risks of venous thrombosis and pulmonary embolism.
- Infections of the lung and urinary tract develop in almost half of patients with GBS in the intensive care unit.
- Prevention and prompt treatment of nosocomial infections are important aspects of care.
- Chest physical therapy and frequent oral suctioning aid in preventing atelectasis in patients with impaired cough and sigh. Skilled nursing care with regular turning and attention to skin, eyes, mouth, bowel, and bladder are essential. Exposure keratitis is avoided

- Among specific therapeutic interventions aimed at mitigating the harmful effects of autoantibodies, plasma exchange and high-dose intravenous immune globulin (IVIG) infusions five daily infusions of immunoglobulin (0.4 g/kg/day) given in the first 2 weeks of the disease have been shown to be equally effective.
- Benefits are clearest when plasma exchange is begun within 2 weeks of onset. The recommended plasmapheresis schedule entails a series of five exchanges (40 to 50 mL/kg) with a continuous flow machine on alternate days using saline and albumin as replacement fluid.

❖ ***Diabetic Neuropathies***

- The complications specific to diabetes include retinopathy, nephropathy, and neuropathy. Patients with all forms of diabetes of sufficient duration, whether insulin-dependent (IDDM) or non-insulin–dependent diabetes (NIDDM), are vulnerable to these complications.
- Diabetic neuropathy is defined as the presence of symptoms and signs of peripheral nerve dysfunction in individuals with diabetes *after the exclusion of other causes.* In addition, diabetic neuropathies, being common disorders, may coincide with other conditions that cause similar manifestations including CIDP, vitamin B12 deficiency, alcoholic neuropathy, and endocrine neuropathies.

Classification of Diabetic Neuropathies

- ***SYMMETRICAL POLYNEUROPATHIES***

1. Distal sensory or sensorimotor polyneuropathy
2. Small-fiber neuropathy
3. Autonomic neuropathy
4. Large-fiber neuropathy

- ***ASYMMETRICAL NEUROPATHIES***

1. Cranial neuropathy (single or multiple)
2. Truncal neuropathy (thoracic radiculopathy)
3. Limb mononeuropathy (single or multiple)
4. Lumbosacral radiculoplexopathy (asymmetrical proximal motor neuropathy)
5. Entrapment neuropathy

- ***COMBINATIONS***

1. Polyradiculoneuropathy
2. Diabetic neuropathic cachexia
3. Symmetrical polyneuropathies

❖ ***Pathogenesis of Diabetic Neuropathy***

- Although the causes of diabetic neuropathies remain unknown, currently accepted hypotheses focus on the possibilities of metabolic and ischemic factors and their interactions in causing nerve injury.
- Hyperglycemia has been implicated in many different pathogenic mechanisms in diabetic neuropathy, but there is also a role for insulin defciency and its effect on neurotrophic factors in the pathogenesis of neuropathy.
- Hyperglycemia generates rheological changes that increase endoneurial vascular resistance and reduce nerve blood flow. Hyperglycemia also causes depletion of nerve myoinositol through

a competitive uptake mechanism and activates protein kinase C. reductase, which leads to the accumulation of sorbitol and fructose in nerve and enhancement of non enzymatic glycosylation of structural nerve proteins. Another adverse effect of hyperglycemia is autooxidation of glucose, which results in the generation of toxic reactive oxygen intermediates.

❖ ***Clinical Feature***

1. Distal Symmetrical Polyneuropathy

- Distal symmetrical polyneuropathy is the most common form of diabetic neuropathies. Many physicians incorrectly assume that the term *diabetic neuropathy* is synonymous with distal symmetrical polyneuropathy, because the latter constitutes perhaps three fourths of all diabetic neuropathies. In distal symmetric polyneuropathy sensory deficits predominate, and autonomic symptoms usually correlate with the severity of the neuropathy.
- Most patients will develop only a minor motor involvement affecting the distal muscles of the lower extremities.
- Sensory disturbances have a stocking-glove distribution followinga length- dependant pattern. Early sensory manifestations begin in the toes, gradually spreading proximally; when these reach above knee level, the fi ngers and hands become affected.
- The distal symmetrical polyneuropathy may be subclassified further into two major subgroups, depending on the nerve fiber type most involved: large-fiber and small-fiber variants.
- The large-fiber variant presents with painless paresthesias beginning at the toes and feet, impairment of vibration and joint position sense, and diminished muscle stretch refl exes. In advanced cases, significant ataxia may develop due to sensory deafferentation.

- In contrast to the large-fiber neuropathy, the small-fiber variant frequently presents with pain of a deep, burning, stinging, aching character, often associated with spontaneous shooting pains and allodynia to light touch. Pain and temperature modalities are impaired with relative preservation of vibration and joint position sensation and muscle stretch reflexes. The small fiber variant is often accompanied by autonomic neuropathy
- At times, a painful small-fiber neuropathy develops soon after the onset of IDDM.

- It is now clear that peripheral neuropathy can occur before the onset of clinically diagnosable diabetes mellitus, so-called *impaired glucose tolerance neuropathy*. Individuals with impaired glucose tolerance, as determined by oral glucose tolerance testing (OGTT), have been demonstrated to have symptoms, electrophysiological abnormalities, and intraepidermal nerve fiber density reduction consistent with a predominantly small-fiber neuropathy, although with changes less pronounced than in their diabetic counterparts
- The implication for clinical practice is that patients with undiagnosed painful peripheral neuropathy should undergo OGTT and that early diagnosis followed by improved life-style may result in reversal of impaired glucose tolerance and, *intuitively,* of neuropathy.
- An acute painful neuropathy may be precipitated following the initiation of treatment of a diabetic patient with insulin(*treatment-induced neuropathy*). Burning pain and paresthesias develop in the distal lower extremities shortly after the establishment of glucose control. Pain persists for weeks or up to several months with spontaneous resolution to follow.

2. Diabetic Autonomic Neuropathy

- Autonomic neuropathy usually correlates with the severity of somatic neuropathy. The spectrum of autonomic involvement ranges from subclinical functional impairment of cardiovascular reflexes and sudomotor function to severe cardiovascular,gastrointestinal, or genitourinary autonomic dysfunction.

- Orthostatic hypotension (rarely symptomatic), resting tachycardia, or diminished heart rate response to respiration are the hallmarks of diabetic cardiac autonomic neuropathy. Orthostatic hypotension occurs mainly because of failure of the sympathetic nervous system to increase systemic vascular resistance in the erect posture and impairment of compensatory cardiac acceleration.
- Vagal denervation of the heart results in a high resting pulse rate and loss of sinus arrhythmia.
- An increased incidence of painless or silent myocardial infarction is reported in diabetic patients with autonomic neuropathy.
- Gastrointestinal motility abnormalities involving esophagus, stomach, gallbladder, and bowels and fecal incontinence may occur.

- Delayed gastric emptying, usually of solids, leads to nausea, early satiety, and postprandial bloating.
- Diabetic diarrhea, due to small intestinal involvement, typically occurs at night, and is explosive and paroxysmal. However, constipation due to colonic hypomotility is more common than diarrhea.. Bacterial overgrowth may occur and can often be successfully treated with small doses of tetracycline (250 to 500 mg/day in a single dose given at the onset of a diarrheal attack) in adult patients.
- Bladder atony leads to prolonged intervals between voiding, gradually increasing urinary retention, and finally overflow incontinence. The symptoms of urinary autonomic dysfunction develop insidiously and progress slowly.
- Autonomic dysfunction involves both erectile failure and retrograde ejaculation.

3. Asymmetrical Proximal Diabetic Neuropathy or Lumbosacral Radiculoplexopathy

- Diabetic amyotrophy, thoracic radiculopathy, and proximal or diffuse lower extremity weakness should probably be grouped under the single term *diabetic polyradiculopathy,* since these disorders seem to be different presentations of the same basic involvement of multiple nerve roots or proximal nerve segments.
- Clinically, asymmetrical weakness and wasting of pelvifemoral muscles may occur either abruptly or in a stepwise progression in individuals with diabetes who are older than 50 years. Most patients have NIDDM, but the onset is unrelated to the duration of diabetes.
- Typically, unilateral severe pain in the lower back, hip, and anterior thigh heralds the onset of neuropathy. Within days to weeks weakness ensues, affecting proximal and, to a lesser extent, distal, lower extremity muscles (iliopsoas, gluteus, thigh adductor, quadriceps, hamstring, and anterior tibialis). In some cases, the opposite leg becomes affected after a latency of days to months. Reduction or absence of knee and ankle jerks is the rule. Numbness or paresthesias are minor

4. Truncal Neuropathy

- Diabetic truncal neuropathy or thoracic radiculopathy involving the T4 through T12 spinal nerve roots causes pain or dysesthesias in areas of the chest or abdomen, thereby producing diagnostic confusion. Bulging of the abdominal wall as a result of weakness of abdominal muscles may also occur .This unique truncal pain is seen in older patients with NIDDM and may occur either in

isolation or together with the typical lumbosacral radiculoplexopathy.

- Patients describe burning, stabbing, boring, beltlike pain. Contact with clothing can be very unpleasant. The onset may be either abrupt or gradual and in some patients preceded or accompanied by a profound weight loss.

5. Cranial Mononeuropathies

- A third-nerve palsy is the most commonly encountered diabetic cranial mononeuropathy. Pupillary sparing, the hallmark of diabetic third-nerve palsy, results from ischemic infarction of the centrifascicular oculomotor axons due to diabetic vasculopathy of the vasa nervorum. The peripherally located pupillary motor fibers are spared as a result of collateral circulation from the circumferential arteries.
- With decreasing frequency, the fourth, sixth, and seventh nerves are also affected. Patients with Bell's palsy have a significantly higher frequency of diabetes than an age-matched population. Most make a full recovery in 3 to 5 months.
- Two serious infectious syndromes occur occasionally in patients with diabetes mellitus, which characteristically affect one or more cranial nerves by local inflammation. Rhinocerebral mucormycosis and "malignant" external otitis were often fatal before the advent of early diagnosis and effective treatment.

Treatment

- The cornerstone in the treatment of diabetes and its complications remains optimal glucose control. Considerable evidence supports the idea that good diabetic control is associated with less frequent and less severe peripheral nerve complications.
- Successful pancreatic transplantation is beneficial in preventing the progression of diabetic neuropathy, and the effect may be sustained in long-term follow-up
- Clinical trials of myoinositol supplementation have shown confl icting results, and those of aldose reductase inhibitors have so far failed to produce convincing clinical improvement or proved toxic, though there were modest changes in nerve conduction and nerve pathology.
- Based on experimenttal data suggesting that oxidative stress mediated by free radical species may be involved in diabetic

neuropathy, two large multicenter, randomized, controlled clinical trials of a-lipoic acid, either oral or intravenous, showed benefit in reducing neuropathic symptoms and deficits.

- Symptomatic treatment for pain, autonomic manifestations, and the complications of sensory loss can be offered to mitigate the impact of neuropathic symptoms. It should be remembered that about 20% of patients with chronic painful diabetic neuropathy of over 6 months' duration demonstrate a complete remission of symptoms over time.
- Patients with symptomatic orthostatic hypotension are advised to sleep with the head of the bed elevated 6 to 10 inches. The head-up tilt prevents salt and water losses during the night, and will combat supine hypertension.
- Practical suggestions include drinking two cups of strong coffee or tea with meals, eating more frequent small meals rather than a few large ones, and increasing the daily fluid intake (>20 oz/day) and salt ingestion (10 to 20 g/day). Elastic body stockings may be benefi cial by reducing the venous capacitance in bed but are poorly tolerated by many patients. Plasma volume expansion can be achieved by fludrocortisone (0.1 to 0.6 mg/day).

❖ ***Niacin Deficiency (Pellagra Neuropathy)***

- Niacin (nicotinic acid, vitamin B3), an end-product of tryptophan metabolism, is incorporated into the coenzymes nicotinamide adenine dinucleotide (NAD) and NADPH and their reduced forms. These coenzymes play important roles in carbohydratemetabolism.
- Dietary defi ciency of niacin is rare in developed countries, but is seen in populations dependent on corn (maize) as the main source of carbohydrate because corn contains little niacin or tryptophan. Defi ciency of niacin leads to pellagra, which affects the ***gastrointestinal tract, skin, and nervous system***, resulting in the triad of ***dermatitis, diarrhea, and dementia (3Ds***).
- A distal sensorimotor polyneuropathy develops in 40% to 56% of patients with pellagra, and, if diarrhea and skin changes are absent, is clinically indistinguishable from thiamine-defi ciency neuropathy.
- Nonendemic pellagra rarely occurs in patients with alcoholism or malabsorption. Excessive conversion of tryptophan to serotonin in carcinoid syndrome also results in niacin deficiency and pellagra.

- Deficiency of vitamin B6 and diets rich in neutral amino acids that interfere with tryptophan metabolism may also cause niacin deficiency.
- Oral nicotinic acid (50 to 250 mg/day) is sufficient to treat most symptomatic patients. However, the response to treatment may be incomplete.

❖ ***Vitamin B12 Deficiency Polyneuropathy: Subacute Combined Degeneration***

- Cobalamin (vitamin B12) and folate are essential vitamins necessary for effective DNA synthesis. Impaired DNA synthesis could interfere with oligodendrocyte growth and myelin formation.
- Animal products (meat, poultry, fish, and dairy products) are the primary dietary source of cobalamin. The average Western diet provides an excess of the vitamin (daily requirement, 3 to 9 mg), which is stored in the liver. Excessive intake of vitamin B12 has not been associated with any adverse effect.
- Within the acid environment of the stomach cobalamin is released from dietary proteins. Free cobalamin initially binds to glycoproteins known as R-binders, which are secreted by salivary glands and gastric mucosa. In the duodenum the cobalamin- R-binder complex is degraded by pancreatic enzymes, and the released cobalamin then binds avidly to intrinsic factor, a 60-kD glycoprotein produced by gastric parietal cells. The vitamin B12-intrinsic factor complex is absorbed by means of binding to intrinsic factor receptors in the terminal ileum. A small portion of ingested cobalamin is also absorbed by passive diffusion.

- Cobalamin deficiency is common in the elderly and mainly produces **pernicious anemia**. This results from lack of intrinsic factor caused by progressive autoimmune **destruction of parietal cells** in the gastric mucosa. Acquired malabsorption of vitamin B12 may occur also following **gastric and terminal ileal resection** and in the setting of a wide range of gastrointestinal disorders. However, due to the large stores of cobalamin in the body it may take several years before the symptoms of deficiency develop after these surgeries. Unusual causes include **dietary insufficiency in strict vegetarians (vegans)** and intestinal infection with fish tapeworms.. A low level of cobalamin may be seen in **pregnancy**, **oral contraceptive** and **anticonvulsants** use, and in **multiple**

myeloma. Intraoperative use or recreational abuse of **nitrous oxide**, which inactivates cobalamin-dependent enzymes, may cause acute or subacute vitamin B12-dependent neurological disease, particularly in patients with marginal cobalamin stores. **Prophylactic B12 injections given weeks before anesthesia will prevent the neurological deterioration**.

- The full-blown clinical picture of vitamin B12 defi ciency consists of macrocytic anemia, atrophic glossitis, and peripheral and central neurological complications. These last conditions include **peripheral neuropathy** and **optic atrophy**, as well as lesions in the **posterior and lateral columns of the spinal cord** (subacute combined degeneration of the spinal cord) and in the brain.
- The neurological dysfunction may be the earliest and often the only manifestation of vitamin B12 defi ciency. The peripheral neuropathy results in paresthesias and large-fiber modality sensory loss (vibration and proprioception), which may begin or be prominent in the hands. The spinal cord manifestations consist of posterior column damage particularly of thoracic and cervical cord, which may include a truncal sensory level, and upper motor neuron signs of limb weakness, spasticity, and extensor plantar responses. The dorsal columns of the spinal cord may show a decreased signal on T1- and increased signal on T2-weighted MRI images and temporary contrast enhancement involving the dorsal and lateral column may be present.

- Cerebral involvement ranges from subtle behavioral changes and forgetfulness to dementia or stupor.
- An unsteady gait, positive Romberg's sign reflecting a sensory ataxia, diffuse hyperreflexia, and absent ankle jerks should raise the suspicion of cobalamin deficiency.
- The diagnosis is confirmed by low serum vitamin B12 levels (<170 pg/mL) and normal serum folate concentration.

- Initial treatment consists of daily intramuscular injections of 1 mg of cyanocobalamin or hydroxycobalamin for the first week, followed by weekly injections of 1 mg, until 12 doses have Maintenance schedules of monthly injections of 100 mg or 1 mg every 3 months have been found satisfactory in preventing relapses.
- This treatment corrects the anemia and may reverse the neurological complications completely if given soon after their

onset. Major neurological improvement can be expected to occur during the first 3 to 6 months of therapy.

❖ ***Neuropathy Associated with Mycobacterium leprae***

- Hansen's disease (leprosy) is a major cause of neuropathy worldwide, especially in tropical and subtropical regions. As improvements in public health and use of multidrug therapy have advanced, the prevalence of Hansen's disease in the world, as estimated by the World Health Organization (WHO), has dropped from 5.1 million in 1987 to less than 500,000 atthe beginning of the year 2004.
- Leprosy remains a major challenge in the field of microbiology, pathology, immunology and genetics, as *Mycobacterium leprae* cannot be cultivated in the lab, generates an extraordinary range of cellular immune responses, and only a small portion of any given population is susceptible to its infection.
- *M. leprae* is thought to be transmitted through the upper respiratory tract. The nasal secretions of those with lepromatous leprosy may contain up to 2 μ 108 *M. leprae* in a single nose blow. Particularly vulnerable tissue are those with mean daily temperatures in the 27° to 30°C range, as this promotes more rapid bacterial growth.
- The skin and superficial nerve trunks of patients with leprosy are particularly vulnerable, leading to cutaneous lesions, anesthesia, and paralysis of face and limb muscles. The disease is classifi ed by host reaction to infection into two polar forms, tuberculoid and lepromatous, with three intermediate forms termed *borderline tuberculoid*, *intermediate borderline*, and *borderline lepromatous*. The Hansen bacillus has a proclivity for Schwann cells, which may serve as a sequestered reservoir of infection with relative protection from host defenses. The neuropathy arises not only from the infection of peripheral nerves but also from the inflammatory and immunological responses to this mycobacterium.

Clinical Features

- The unique propensity of *M. leprae* to invade cutaneous nerves and nerve trunks causes the cardinal symptom of sensory loss.
- In tuberculoid Hansen's disease sensory loss, initially affecting pinprick and temperature, is detected within sharply demarcated hypopigmented skin lesions. Adjacent cutaneous nerves or mixed nerve trunks are apt to become involved. The body folds, being warmer than exposed areas, are not affected. Proprioception and motor function are largely unaffected in the early stages, so

patients can still use their anesthetic limbs, which leads to painless trauma, ulcerations, and trophic changes. Attention should be paid to the palpation of peripheral nerves that course close to the skin surface, including the great auricular, ulnar, radial, common fi bular, and sural nerves, in order to detect nerve enlargement.

- Lepromatous Hansen's disease is characterized by symmetrical bacillary infiltration of the skin with a predilection for cooler areas of the body, avoiding the scalp, palms, soles, and midline of the back. The skin may have multiple nodules, papules, macules, and ulcerations, or there may be diffuse cutaneous involvement with a waxy, myxedema-like appearance.
- Similarly, the distribution of sensory loss is related to the local skin temperature, the coolest parts such as the pinna of the ear; the tip of the nose; malar areas of the face; dorsal surfaces of the hands, forearms, and feet; and dorsolateral surfaces of the lower legs being affected first. Because of the minimal inflamatory response, nerve trunk involvement occurs late in this form.
- Commonly affected nerves include the ulnar, common peroneal, and superficial branches of the facial and median nerves, in that order.
- The selective involvement of small branches of the facial nerve leads to the typical patchy nature of facial paralysis with early weakness of medial forehead elevators.

Treatment

- Management consists of specific chemotherapy and prevention and treatment of deformities.
- The current recommendation for paucibacillary infections (those classified as indeterminate, tuberculoid, or borderline tuberculoid Hansen's disease) is the combination of dapsone, 100 mg/day, and rifampin, 600 mg/day, for at least 6 months, followed by dapsone monotherapy for 3 to 5 years.
- Patients with multibacillary infections (borderline or lepromatous leprosy) receive the same combination therapy, with the addition of clofazimine (50 mg/day). Treatment is continued for a minimum of 2 years or until skin smear results are negative.
- For dapsone-resistant strains or patients with glucose-6-phosphate dehydrogenase deficiency, clofazimine and rifampin are used together, with consideration of a third agent, either ofloxacin (400 mg/day), clarithromycin (250 mg twice a day), or minocycline (100 mg/day). The reactions need to be treated immediately with high doses of corticosteroids.

Epilepsy

(Dr.Aktham Alemam)

Definition

- It is a chronic disease characterized by recurrent stereotyped seizures without provocation.
- A seizure is a transient disturbance of cerebral functions caused by abnormal neuronal electrical discharge.

Prevalence

- It occurs in 0.4- 1% of the population.
- More common in the first decade of life and after the age of 65 years.

Pathogenesis

Epilepsy may be secondary to either:-
1-Abnormal neuronal membranes.
2- Imbalance between excitatory and inhibitory influences.

Etiology

1- Idiopathic: No apparent cause. It is secondary to an abnormality of genes. This leads to abnormal neurotransmitter receptors.

2- Symptomatic: Secondary to brain pathology e.g trauma, tumor, etc .

Clinical Classification of Epilepsy

1- Generalized epilepsy :-

- Tonic - Clonic - Tonic-Clonic
- Atonic - Myoclonic - Absence

2- Partial epilepsy:-

- Simple partial.
- Complex partial.

- Partial with secondary generalization.

3- Unclassified epilepsy.

Clinical Picture

The diagnosis of epilepsy is mainly clinical. The clinical presentation depends on its type.

A- Generalized Epilepsy

1- Absence epilepsy

- Common in *infancy and childhood* (rare after age of 18 years old).
- It is usually *idiopathic*.
- Characterized by sudden brief attacks of loss of consciousness .
- No aura , convulsions, or post-ictal phenomena.
- There is stopping of motor activity but the postural functions of the brain are preserved (i.e no falling).
- The attacks are frequent (may be 100 times/day) and each lasts for 5-15 seconds.

2- Generalized tonic-clonic epilepsy

Prodroma:-

- It occurs in some patients, few hours or a day before the fit, denoting that the fit is expected .
- It may be: - Psychological (e.g depression or anxiety).
  - Sensory (e.g headache).
  - Motor (e.g myoclonic jerks).

The fit has 3 stages:-

Aura:-

- Present in 50% of patients.
- It is a symptom produced by the beginning of the discharge and points to the site of the epileptic focus.
- It is too brief for the patient to save himself from falling comatose.

The convulsive stage:-

It starts with loss of consciousness and is divided into 2 phases:-

1- Tonic phase:- (½ minute)

- Epileptic cry: due to the forcible expulsion of air through the partially closed vocal cords.
- All voluntary muscles become rigid →
  Head retraction and opisthotonus position.
  U L:- Adduction and flexion. L.L:- Extension.
  Respiratory muscles→ cyanosis.
- The powerful tonic spasm may lead to dislocation of joint (e.g shoulder) or fracture of bone (e.g vertebra).

Clonic phase:- (1-2 minutes)

- The clonic jerks of the muscles → re-entry of air into the lung → ↓ cyanosis, and expired in short puffs mixed with saliva → mouth froth.
- Tongue or cheeks biting → staining the froth with blood.
- Emptying of the bladder, if it is full.

The post-convulsive stage (from few minutes to half an hour)

Flaccid coma → dilated pupils , lost corneal and tendon reflexes, and extensor plantar reflex on both sides.

On awaking the patient may have :-

- Severe fatigue and go into deep sleep (or pass directly from coma to sleep).
- Headache and vomiting.
- Post-epileptic automatism.

3- Myoclonic seizures

- Bilateral brief shock-like jerks of muscles for less than one second.
- The consciousness is preserved.
- More on awaking up or falling asleep.

B-Partial Seizures

1-Complex partial seizures

- Present in 40% of cases of epilepsy in adults.
- The central feature of complex partial seizure is *impairment of consciousness* .
- It may or may not be preceded by symptoms and signs of simple partial

seizure.
- It may or may not be associated with automatisms.

2- Simple partial seizures

- They are caused by local cortical discharge (70% temporal, 20%frontal, and 10% others).

- Seizure symptoms depend on the site of epileptic focus, *without* impairment of consciousness.

a. Motor signs.

- The *most frequent* type of simple partial seizures.
- The convulsions affect mostly the face and upper limb, but may spread to lower limbs.

b. somatasensory or special sensory symptoms

- It is rare, 2% of epileptic patients.
- It may be somatosensory as numbness, tingling, needles or weak electric sensation
- It may be visual flashes or olfactory odors.

c- Autonomic.

e.g Recurrent sudden attacks of epigastric or abdominal pain (most common type, and ascends to throat), flushing or pallor, diaphoresis, vomiting, sphincters disturbances

d- Psychic: Abnormal attacks of unexplained fears or laughter

Investigations

Epilepsy is a clinical diagnosis.

1- EEG:

- The diagnosis of epilepsy is usually confirmed by EEG.
- The most specific epileptic discharges are spikes (or sharp waves) and slow wave complexes.

- The first EEG is positive in only 50% of epileptic patients when recorded in the interictal state. So , initial negative EEG does not exclude epilepsy. Repeated EEG proves positive in about 90% of cases.

2- MRI- Brain : for underlying structural lesions.

3- Laboratory:

- To exclude other causes of convulsions eg , metabolic, toxic…….etc
- For monitoring the serum level of antiepileptic drugs.

Differential diagnosis of epilepsy

Epileptic seizures should be differentiated from other paroxysmal cerebral dysfunctions e.g syncopal attacks, febrile convulsions , pseudoseizures.

Pseudoseizures:

- The attacks occur in front of others, to gain their attention
- No harm , no injury, no urine incontinence.
- No true loss of consciousness, no post-ictal confusion.
- EEG during the attack does not show epileptic dischrarge.

When to start TTT?

- The patient should have 2 fits to start medical treatment. The interval between the 2 fits must be short (6-12months).
v - About ¾ of persons who have one seizure never have another.
- There are risk factors of recurrence of the second fit
- 2 or more factors : 100% chance of recurrence within 2 years. So, *patients with one fit plus 2 or more risk factors should be treated.*

- Risk Factors (If there is single epileptic fit only) :
  1- Positive family history.
  2- Partial seizure type.
  3- Post-ictal motor paralysis.
  4- Abnormal EEG.
  5- Evidence of structural lesion (strongest factor).

General principles of TTT

1- *Accurate **diagnosis** of epilepsy and its type* e. g carbamazepine and vigabatrine may exacerbate absence and myoclonic epilepsy.

2- *Start with **monotherapy*** as:

- It controls 70-90% of patients.
- Polytherapy → unnecessary side effects.

3- *Start with the **drug of first choice***.

4- *Start with **minimum effective dose**:* if seizures persist, increase the dose until the seizures are controlled or side effects appear.

5- If no side effects, the drug shouldn't be considered ineffective until the **plasma level** of the drug documented that it reached the highest therapeutic concentration.

Categories of AEDs

1- Brood-spectrum AEDs : e.g valproate, Benzocliazepines, Barbiturates, lamotrigine, topiramate.

2- Against partial, CPS (± 2ry generalization) or primarily generalized.

- e. g carbamazepeine, plenytoin, gabapentin, tiagabine

- These drug are not effective or even worsen other types of generalized epilepsy e. g absence epilepsy and myoclonic epilepsy).

3- Others not fulfilling the criteria mentioned before: e. g Etheusuximide: → Absence.

Anti.epileptic drugs of choice

a- Partial epilepsy: Carbamazepine.

b- Generalized tonic-clonic epilepsy (GTC):

Valproate: The most effective and broad spectrum

If GTC+ absence → valproarte is the first choice.

c- Absence epilepsy: Ethosuximide .

d- **Unclassified epilepsy:**

Brood spectrum AED e. g valproate, lamotrigine.

Antiepileptic drug withdrawal

- After *2-3 years free* of seizures on AEDs, discontinuation of TTT can be made.
- About 80% of recurrence occurs in the *first 4 months* after stopping TTT. So, dangerous activities should be avoided during this period.
- Withdrawal can be over *6 weeks or 9 months* (but average is 2-3 months).

Status Epileptics

- **Definition:** 30 or more minutes (some consider it 5-10 min) of continuous or recurrent seizures without recovery to baseline function.
- It is the most common neurological emergency and the *mortality ranges from 2-3% in children and 30% of adults*

- **Causes:**

Any of the causes of acute symptomatic seizures.
Most common causes are (AED withdrawal – Fever).

Treatment

0 - 10 min

- Nasal o_2 and insert airway if necessary.
- Take history and examine the patient.
- IV line to a) Draw blood sample for glucose, AEDs, renal, liver, ca and Mg.

b) give 50 ml of 50% glucose + 100 mg thiamine (to avoid wernick's encephalopathy).

10- 30 min

- Lorazepam 0.1 mg / kg or diazepam up to 20 mg + simultaneous phenytoin 20 mg / kg (or phosphenytion) at a rate of 50 mg / min.
- Monitor ECG and B.P.

30-60 min

Additional 5 – 15 mg / kg fosphenytoin (20 mg / kg) with 50 mg / min.

At 60 min

Anaesthesia with Phenobarbital 5 – 15 mg / kg until epileptic activity is clearly suppressed.

Table of anti-epileptic drugs:

Side Effects	Dose	Drug
Hepatotoxicity, pancreatitis, tremors, weight gain and hair loss	15-60 mg/kg	**Valproate (Depakine)**
Sedation, hypersensitivity, hepatotoxicity, pancytopenia, hyponatremia	15-25	**Carbamazepine (Tegretol)**
Hirsiutism, gingival hyperplasia, coarse features of the face(lion face), ataxia	3-7 mg/kg	**Phenytoin (Epanutin)**
Sedation, dependence, tolerance	0.5-4 mg/d	**Clonazepam (Rivotril)**
Rash, tremors	5-10 mg/kg	**Lamotrrigine (Lamictal)**
Cognitive slowing, renal stones , loss of weight	5-9 mg/kg	**Topiramate (Topamax)**
Somnelence, asthenia, and behavioral changes	20-30 mg/kg	**Levitiracetam (Keppra)**

Epilepsy Surgery

About 5 – 10 % of cases of epilepsy benefits from surgery.

- **Philosophy:-**

Accurate localization of the site of onset of seizures and then

1- Curative TTT : Removal of the area of epileptogenic focus.

2- Palliative TTT: Disconnection of epileptogenic zone to prevent spread of seizures.

- Timing:

If 3 AEDs fail to control epilepsy for 12 – 24 months, epilepsy surgery should be considered immediately.

PARAPLEGIA

(Dr.Aktham Alemam)

* **Definition** : Paraplgia is motor paralysis or paresis of both lower limbs.

Approach to diagnosis of Paraplegia: *

1- Is it paraplegia?

2- Where is the lesion(UMN or LMN)?

3- What is the type of it (Focal, systemic or disseminated)?

* **Exclude other causes of difficulty of walking:-**

1- Painful conditions: e.g polyarthritis.

2- Ataxia : e.g cerebellar lesions.

3-Involuntary movements e.g advanced Parkinson disease or dystonia.

4- Mental retardation.

Causes of paraplegia:

1- Upper motor neuron lesion: (Spinal or cerebral).
2- Lower motor neuron lesion: (AHCs , motor roots or peripheral nerves).

Causes of cerebral paraplegia

A- Parasagittal region:

- Traumatic: e.g Depressed fracture of the skull or parasagittal subdural hematoma.

-Inflammatory: e.g Encephalitis or meningo-encephalitis

- Vascular: e.g Superior sagittal sinus thrombosis

- Neoplastic: e.g Parasagittal meningioma.

B- Brain stem:

e.g Medline brainstem tumors or syringobulbia.

Causes of spinal paraplegia

A-Focal causes

- Compressive

-Vertebral: Fracture, disc prolapse, Pott s disease, tumors as hemangioma or osteosarcoma or metastases.

-Meningeal: Exatr-adural e.g leukemic deposits or intra-dural e.g neurofibroma.

- Cord (Intramedullary): e.g syringomyelia, glioma , or ependymoma.

2-Inflammatory: e.g transverse myelitis.

3- Vascular: e.g anterior spinal artery occlusion.

B- Systemic causes

- Heredofamilial : e.g hereditary spastic paraplegia , Friedriech ataxia.

Symptomatic: e.g subacute combined degeneration.-

Idiopathic: e.g motor neuron disease.-

C- Dissiminated causes

- Multiple sclerosis.

- Disseminated encephalomyelitis.

Clinical picture of focal spinal paraplegia

1- At the level of the lesion:

Localized pain, tenderness, or deformity (If the cause is vertebral).

Radicular manifestations: By affection of the posterior AND/OR anterior roots.

2- Below the level of the lesion:

Motor manifestations :

Acute causes: Stage of flaccidity (due to neuronal shock) , then stage of spasticity after 2-6 weeks.

Gradual causes: Paraplegia in extension then paraplegia in flexion.

Sensory Manifestations

If the cause is extra-medullary → Sensory level.

If the cause is intramedullary → Jacket sensory loss of dissociated nature.

Sphincteric manifestations:

-Acute lesions →Retention of urine in the shock stage followed by precipitancy of micturition.

-Gradual lesions → Precipitancy of micturition.

Causes of flaccid paraplegia

1- Polyradiculopathy.

2- Peripheral neuropathy : e.g GBS, porphyria.

3- NMJ disorders: e.g myasthenia gravis.

4- Muscle disease: e.g muscular dystrophy or acute polymyositis.

Transverse Myelitis

- It is an acute lesion involving the gray and white matter of a limited number of the spinal cord segments.

- Causes:- viral infection, post-vaccination, demyelinating disease.

- Clinical Picture: Upper motor neurone paraplegia with sensory level and sphincteric disturbances.

Investigations: MRI- spinal, CSF. -

Anterior Spinal Artery Occlusion

- Cause: Thrombosis, embolism, or dissecting aortic aneurysm.

- Clinical Picture: As that of the transverse myelitis except the sparing of the deep sensations, as the posterior column of the spinal cord is supplied by the posterior spinal artery.

Syringomyelia

- It is a chronic disease characterized by gliosis and cavitation around the central canal in the gray matter of the spinal cord.

Level: Commonly in the lower cervical and upper thoracic segments .-

- Clinical Picture: Motor: LMN weakness in the ULs, and UMNL in the LLs.

Sensory: Jacket sensory loss of dissociated nature

Autonomic: Trophic ulcers in the fingers and vasomotor changes.

Associated skeletal anomalies as pes cavus and spina bifida.

Investigations: MRI-Spine-

Cauda Equina

It is a collection of lumbo-sacral roots in the lower part of the spinal canal.

Causes of cauda equina lesions:

1- Congenital : Spina bifida

2- Traumatic: Disc prolapse or vertebral fracture

3- Inflammatory: Pott disease.

4- degenerative : Lumbar spondylosis.

5- Neoplastic: Meningioma, metastases.

Clinical Picture:

1- Motor : LMN weakness affecting one or both lower limbs. The weakness is in the muscles supplied by the affected root.

2- Sensory: Painful onset, with radicular parasthesia at onset followed by hypothesia later.

3- Sphincteric disturbances: Late

Invetigations: MRI-Lumbosacral spine.

COMA

(Dr.Rasha Said)

❖ Definition:

It is a prolonged state of unconsciousness (lasting more than six hours) , in which a person: cannot be awakened; fails to respond normally to painful stimuli, light, or sound; lacks a normal sleep-wake cycle; and, does not initiate voluntary actions.

❖ *DD from stupor:*

Stupor is unresponsiveness from which a person can be aroused only by vigorous physical stimulation. Coma is unresponsiveness from which a person cannot be aroused.

❖ *Pathophysiology:*

For a person to maintain consciousness, two important neurological components must function:

1- ***Cerebral cortex***—the gray matter that covers the outer layer of the brain.

2- ***Reticular activating system*** (RAS).

- RAS is a more primitive structure in the brainstem that is tightly in connection with reticular formation (RF).
- The RAS area of the brain has two tracts, the ascending and descending tract.
- Made up of a system of acetylcholine-producing neurons, the ascending track, or ascending reticular activating system (ARAS), works to arouse and wake up the brain, from the RF, through the thalamus, and then finally to the cerebral cortex.
- Injury to either or both of these components is sufficient to cause a patient to experience a coma.

❖ *Classification*:

Glasgow Coma Scale:

- It is a neurological scale that aims to give a reliable, objective way of recording the conscious state of a person for initial as well as subsequent assessment.

- A patient is assessed against the criteria of the scale, and the resulting points give a patient score between 3 (indicating deep unconsciousness) and either 14 (original scale) or 15 (the more widely used modified or revised scale).
- GCS was initially used to assess level of consciousness after head injury, and the scale is now used by first aid, nurses and doctors as being applicable to all acute medical and trauma patients.
- In hospitals it is also used in monitoring chronic patients in intensive care.
- The scale is composed of three tests: eye, verbal and motor responses. The three values separately as well as their sum are considered. The lowest possible GCS is 3 (deep coma or death), while the highest is 15 (fully awake person).

		2	**3**	**4**		**5**	**6**
	ɔes not open eyes	Opens eyes in response to <u>painful stimuli</u>	Opens eyes in response to voice	Opens eyes spontaneously			
	ake: no sounds	Incomprehensible sounds	Utters inappropriate words	Confused, disoriented	Oriented, converses normally		
	ake: no movement	Extension to painful stimuli (decerebrate response)	Abnormal flexion to painful stimuli (decorticate response)	Flexion / Withdrawal to painful stimuli	Localizes painful stimuli	Obeys commands	

<u>Generally, brain injury is classified as</u>:

- Severe, with GCS < 8-9
- Moderate, GCS 8 or 9–12 (controversial)
- Minor, GCS ≥ 13.

- Periods of impaired consciousness can be short or long.
- The degree of impairment can range from slight to severe:
- **<u>Lethargy</u>** is a slight reduction in alertness or mild mental fogginess (clouding of consciousness). People tend to be less aware of what is happening around them and to think more slowly.
- **<u>Obtundation</u>** refers to a moderate reduction in alertness or moderate clouding of consciousness.
- **<u>Altered mental status</u>** is sometimes used by doctors to refer to a change in consciousness, such as lethargy, obtundation, or delirium.

- **Stupor** is an excessively long or deep state of unresponsiveness.

  A person can be aroused from it only briefly by vigorous stimulation, such as repeated shaking, loud calling, or pinching.

- **Coma** is a state of complete unresponsiveness. A person cannot be aroused at all. A person in a deep coma lacks the most basic responses, such as moving a limb away from something that hurts. People may still have reflexes (such as the knee jerk reflex), which are automatic responses to a stimulus and which do not involve the brain

❖ ***Causes of coma:***

- **Traumatic brain injuries**: often caused by traffic collisions or acts of violence, are common causes of comas.
- **Stroke:** Reduced or interrupted blood supply to the brain (stroke), which may be caused by blocked arteries or a burst blood vessel, can result in coma.
- **Tumors**: Tumors in the brain or brainstem can cause coma.
- **Diabetes:** blood sugar levels that become too high (hyperglycemia) or too low (hypoglycemia) can cause a stroke or coma.
- **Lack of oxygen:** People who have been rescued from drowning or those who have been resuscitated after a heart attack may not awaken due to lack of oxygen to the brain.
- **Infections**: as encephalitis and meningitis cause swelling (inflammation) of the brain, spinal cord or the tissues that surround the brain. Severe cases of these infections can result in brain damage or coma.
- **Seizures**: Ongoing seizures may lead to coma.
- **Toxins**: Exposure to toxins, such as carbon monoxide or lead, can cause brain damage and coma.
- **Drugs and alcohol**: Overdosing of drugs or alcohol can result in coma.
- **Metabolic disorders**: hyponatraemia or hypernatraemia and hypothermia or hyperthermia.
- **Endocrine disorders** :as hypothyroidism
- **Other causes**:
- Cardiac arrest.

- Heart or lung disorders(if severe):as severe heart failure , chronic obstructive pulmonary disease, pulmonary edema, pulmonary embolism, and severe and long-lasting asthma attacks.

- Liver and Renal failure.

❖ ***Diagnosis of coma:***

- Diagnosis of coma is simple, but diagnosing the cause of the underlying disease process is often challenging.
- The first priority in treatment of a comatose patient is stabilization following the basic ABCs (standing for airway, breathing, and circulation).
- Once a person in a coma is stable, investigations are performed to assess the underlying cause.
- Investigative methods are divided into physical examination findings and imaging (such as CAT scan, MRI, etc.) and special studies (EEG, etc.)

❖ ***Clinical presentation:***

❖ **Symptoms:**

1) **Consciousness** is impaired to varying degrees. People in a stupor are usually unconscious but can be aroused with vigorous stimulation. People in a coma are unconscious and cannot be aroused
2) **The pattern of breathing** is usually abnormal. People may breathe too rapidly, too slowly, too deeply, or irregularly. Or they may alternate between these abnormal patterns.
3) **Muscles** may remain contracted in unusual positions. For example, decerebrate rigidity, decorticate rigidity or the entire body may be limp. Sometimes muscles contract sporadically or involuntarily.
4) **pupils**: one or both may be widened (dilated) and not react to changes in light. Or the pupils may be tiny. The eyes may not move or may move in abnormal ways.
5) The disorder that is impairing consciousness may cause other symptoms. For example, if the cause is meningitis (infection of the fluid-filled space within the layers of tissue covering the brain and spinal cord), symptoms may include fever, vomiting, headache, and a painful, stiff neck that makes lowering the chin to the chest difficult or impossible.

❖ Initial assessment and evaluation:

1) Detection and treatment of any immediate life threatening condition:(as hemorrhage, airway obstruction, hypotension or arrhythmia)
2) 50% dextrose is given intravenous immediately without waiting for blood glucose level determination. Thiamine is given with the glucose to prevent Wernicke-Korsakoff syndrome
3) Assessment of the level of consciousness
4) Assessment of the risk of asphyxia

In those with deep unconsciousness, there is a risk of asphyxia as the control over the muscles in the face and throat is diminished. As a result, those presenting to a hospital with coma are typically assessed for this risk. If the risk of asphyxiation is deemed high, doctors may use various devices (such as an oropharyngeal airway, nasopharyngeal airway or endotracheal tube) to safeguard the airway.

5) Physical examination :

❖ **General examination:**

1) Examination of skin, nails and mucous membranes(cyanosis, pallor, cherry redness ,petechiae, jundice, uraemic frost, hypo or hyperpigmentation, signs of trauma)
2) Examination of breath: (acetone or alcohol)
3) Examination of fundi: (papilloedema, hypertensive or diabetic retinopathy, Roth spots, subhyaloid hemorrhage)

4) Examination of the head, face, and skin for clues to the cause, such as the following:

- *Black eyes, cuts, bruises, or leakage of cerebrospinal fluid (fluid that surrounds the brain) from the nose or ears suggests a head injury.*
- *Needle marks suggest an overdose of a drug, such as heroin.*
- *Rashes often suggest an infection, such as sepsis (a severe blood infection) or a brain infection.*
- *If people have bitten their tongue, seizures may be the cause.*

5) Vital signs:

- **Temperature** (rectal is most accurate): Abnormally high temperature may indicate infection, heatstroke, or an overdose of a drug that stimulates the body (such as cocaine or an amphetamine).
- Abnormally low temperature may indicate prolonged exposure to cold, an hypothyroidism, alcohol intoxication, a sedative overdose or, in older people, infection.
- **Blood pressure**, heart rate (pulse), respiratory rate, and oxygen saturation. They should be evaluated quickly to gain insight into a patient's metabolism, fluid status, heart function, vascular integrity, and tissue oxygenation.
- **Respiratory pattern** (breathing rhythm):it is significant and should be noted in a comatose patient. Certain stereotypical patterns of breathing have been identified including :

- ***Cheyne-Stokes breathing*** is a form of breathing in which the patient's breathing pattern is described as alternating episodes of hyperventilation and apnea. This is a dangerous pattern and is often seen in pending herniations, extensive cortical lesions, or brainstem damage.
- ***Apneustic breathing***: sudden pauses of inspiration and is due to a lesion of the pons.
- ***Ataxic breathing*** is irregular and is due to a lesion (damage) of the medulla.

6) Urinary or fecal incontinence may signify an unwitnessed seizure.
7) Scalp is palpated for signs of trauma
8) Ears and nose examination: for blood or cerebrospinal fluid.
9) Neck examination: resistance for passive neck flexion suggests meningitis or subarachnoid hemorrhage.
10) **Neurological examination**:

❖ **Motor responses**:

- Inspection of limb position and spontaneous movements.(voluntary or involuntary as seizures or myoclonus) .
- Asymmetric movements or postures can indicate either hemiparesis or focal seizures.
- Asymmetry of muscle tone suggests a structural lesion, but may not be clear which side is abnormal.
- Assessment of posture and body habitus .There are often two stereotypical postures seen in comatose patients.
- **Decorticate posturing** is a stereotypical posturing in which the patient has arms flexed at the elbow, and arms adducted toward the body, with both legs extended. it indicates a lesion (a point of damage) at or above the red nucleus.
- **Decerebrate posturing** is a stereotypical posturing in which the legs are similarly extended (stretched), but the arms are also stretched (extended at the elbow). It indicates a lesion at or below the red nucleus. In other words, a decorticate lesion is closer to the cortex, as opposed to a decerebrate cortex that is closer to the brainstem.

- **Pupil assessment**: It is often a critical portion of a comatose examination, as it can give information as to the cause of the coma.

Possible interpretation

Normal eye with two pupils equal in size and reactive to light. This means that the patient is probably not in a coma and is probably lethargic, under influence of a drug, or sleeping.

"Pinpoint" pupils indicate heroin or opiate overdose, and can be responsible for a patient's coma. The pinpoint pupils are still reactive to light, bilaterally (in both eyes, not just one). Another possibility is the damage of the pons.

One pupil is dilated and unreactive, while the other is normal (in this case the R eye is dilated but the L eye is normal in size). This could mean a damage to the oculomotor nerve (CN III) on the right side, or possibility of vascular involvement.

Both pupils are dilated and unreactive to light. This could be due to overdose of certain medications, hypothermia or severe anoxia (lack of oxygen).

- **Eye movements**:

- Abnormal eye movements may be conjugate or dysconjugate
- *Eyes deviated conjugately away from the hemiparetic side*: indicates destructive cerebral lesion on the side towards which the eyes are directed.
- *Eyes deviated conjugately towards the hemiparetic side* :it favors pontine lesion or adversive seizures.
- *Eyes roving from side to side with slow smooth velocity*: indicates non wakefulness and an intact brainstem.
- *Jerky movements* suggests saccades and relative wakefulness.
- *Downward eye deviation* suggests a lesion of the rostral midbrain or thalamus. it may be accompanied by loss of pupillary light reactivity.(perinaud syndrome).
- *Vertical divergence of the eyes* (skew deviation):in brainstem or cerebellar lesions.
- *Ocular bobbing*: conjugate brisk downward eye movements several times per minute .it usually reflects lesion of the pons.
- *Periodic alternating or ping pong gaze*: rapid regular conjugate side to side horizontal movements indicate extensive cerebral or cerebellar lesions with intact brainstem.
- If eye movements are unilaterally or bilaterally limited ,then oculocephalic or caloric test is performed.

- ✓ **Oculocephalic reflex (the doll's eye).**

Method: It is performed to assess the integrity of the brainstem. Patient's eyelids are gently elevated and the cornea is visualized. The patient's head is then moved to the patient's left, to observe if the eyes stay or deviate toward the patient's right; same maneuver is attempted on the opposite side. If the patient's eyes move in a direction opposite to the direction of the rotation of the head, then the patient is said to have an intact brainstem. However, failure of both eyes to move to one side, can indicate damage or destruction of the affected side. In special cases, where only one eye deviates and the other does not, this often indicates a lesion (or damage) of the medial longitudinal fasciculus (MLF), which is a brainstem nerve tract.

Caloric reflex test also evaluates both cortical and brainstem function; Method: cold water is injected into one ear and the patient is observed for eye movement; if the patient's eyes slowly deviate toward the ear where the water was injected, then the brainstem is intact, however failure to deviate toward the injected ear indicates damage of the brainstem on that side. Cortex is responsible for a rapid nystagmus away from this deviated position and is often seen in patients who are conscious or merely lethargic.

Assessment of cranial nerves :

- Due to the unconscious status of the patient, only a limited number of the nerves can be assessed. These include CN II,CN III, CN V, CN VII and CN IX, CN X.
- Gag reflex helps assess cranial nerves 9 and 10.
- Pupil reaction to light is important because it shows an intact retina, and CN II; if pupils are reactive to light, then that also indicates that the CN III (or at least its parasympathetic fibers) are intact.
- Corneal reflex assess the integrity of cranial nerves VII and V. Cranial nerve V and its ophthalmic branch (V_1) are responsible for the afferent arm of the reflex, and the cranial nerve VII is responsible for the efferent arm, causing contraction of the muscle orbicularis oculi resulting in closing of the eyes.

❖ ***Investigations:***

a) Laboratory tests:

- Blood levels of sugar, sodium, calcium, alcohol, oxygen, and carbon dioxide.
- Complete blood count: Red and white blood cell counts are determined.
- liver function tests.
- Kidney function tests.

- Blood and urine analysis: to determine whether any commonly used or suspected toxic substances are present.
- Arterial blood gases: oxygen level in blood with a sensor placed on a finger (called pulse oximetry). They also measure levels of oxygen, carbon dioxide, and sometimes other gases in a sample of blood withdrawn from an artery (arterial blood gas tests). These tests are done to check for heart and lung disorders and for possible carbon monoxide poisoning.
- Blood and CSF cultures.

b) Electroencephalogram:(EEG):

- mainly to identify nonconvulsive seizure.
- it can distinguish coma from psychic unresponsiveness or locked in syndromes.

c) Computerized tomography(CT) or Magnetic resonance imaging(MRI):

- It is performed promptly in patients with unexplained coma.
- Computerized tomography (CT scan). CT scan can show a brain hemorrhage, tumors, strokes and other conditions. This test is often used to diagnose and determine the cause of coma.
- Magnetic resonance imaging (MRI). An MRI can detect brain tissue damaged by an ischemic stroke, brain hemorrhages and other conditions. MRI scans are particularly useful for examining the brainstem and deep brain structures.

d) Spinal tap (lumbar puncture) :

- Can check for signs of infections in the nervous system.
- CT or MRI of the head is often done before the spinal tap to determine whether pressure inside the skull is increased—for example, by a tumor or bleeding within the brain (intracerebral hemorrhage). If pressure is increased, a spinal tap could make the brain shift downward by rapidly reducing the pressure below the brain and thus, at least theoretically, cause or worsen brain herniation.

❖ ***Treatment:***

- Medical treatment:

1) Admission in ICU.

2) Stabilization of the patient: The first steps in treatment, sometimes done by emergency medical personnel, are to check whether the airway is open, whether breathing is adequate, and whether pulse, blood pressure, and heart rate are normal (to make sure blood is reaching the brain).

- *If possible, any problems present are corrected by using intubation and ventilation, administration of intravenous fluids or blood and other supportive care as needed.*

3) Maintaining the health of patient's physical state.

- Prevention of infections such as pneumonias, bedsores (decubitus ulcers), and providing balanced nutrition.
- These infections may appear from the patient not being able to move around, and being confined to the bed.
- The nursing staff moves the patient every 2–3 hours from side to side and depending on the state of consciousness sometimes to a chair. The goal is to move the patient as much as possible to try to avoid bedsores, atelectasis and pneumonia.

Pneumonia can occur from the person's inability to swallow leading to aspiration, lack of gag reflex or from feeding tube, (aspiration pneumonia).

4) Comatozed patients may become restless so, special care is needed to prevent them from hurting themselves. Patients who are restless may also try to pull on tubes or dressings so soft cloth wrist restraints may be put on. Side rails on the bed should be kept up to prevent the patient from falling.

5) Treatment of the cause:

- ***Low blood sugar level***, glucose (a sugar) is immediately given intravenously. Giving glucose often results in instant recovery if the coma is caused by a low blood sugar level. Thiamin is always given with glucose because if people are undernourished (usually because of alcohol abuse), glucose alone can trigger or worsen a brain disorder called Wernicke encephalopathy .
- If ***opioid toxication*** is suspected, the antidote naloxone may be given

- If the cause is a ***head injury***, the neck must be immobilized until doctors can check for damage to the spine. People in a deep stupor or a coma after a head injury sometimes benefit from treatment with amantadine
- Rarely, when doctors suspect that ***certain toxic substances*** have been ingested within about 1 hour, they may insert a large tube through the mouth and into the stomach so that the stomach can be pumped. Pumping the stomach is done to identify its contents and to prevent more of the substances from being absorbed. Activated charcoal may also be given through the tube or through a smaller tube inserted through the nose (nasogastric tube). The charcoal prevents the stomach from absorbing more of the substances
- If findings suggest that ***the pressure within the skull is increased***, particularly if doctors suspect brain herniation, doctors may drill a small hole in the skull and insert a pressure-monitoring device into one of the fluid-filled spaces (ventricles) in the brain.
- <u>If the pressure is increased, the following measures may be taken to lower it</u>:
  a) The head of the bed may be elevated.
  b) Diuretics or other drugs may be used to reduce fluids in the brain and rest of the body.
  c) A sedative may be given to control excess involuntary muscle contractions, which can increase pressure within the skull.
  d) Blood pressure is sometimes lowered, particularly if it was already high.
  e) If other measures do not work, the skull may be opened surgically, creating more room for the swollen brain and thus reducing pressure on the brain.
- If the cause is a ***brain tumor or abscess***, corticosteroids, such as dexamethasone, may help reduce pressure. However, corticosteroids are not used when increased pressure is caused by certain other disorders, such as intracerebral hemorrhage or a stroke, because corticosteroids may make these conditions worse.

6) Attempt to wake comatose patients:

Some hospitals treat their patients by either reversing the cause of comatose (i.e., glucose shock if low sugar), giving medication to stop brain swelling, or inducing hypothermia. Inducing hypothermia on comatose patients provides one of the main treatments for patients after suffering from cardiac arrest. In this treatment, medical personnel expose patients to "external or intravascular cooling" at 32-34 °C for 24 h.; this treatment cools patients down about 2-3 °C less than normal body temperature.

❖ ***Long-term care:***

1) Care of feeding:

By a tube inserted through the nose and into the stomach. Sometimes they are fed through a tube (called a percutaneous endoscopic gastrostomy tube, or PEG tube) inserted directly into the stomach through an incision in the abdomen. rugs may also be given through this tube

2) Care of eyes: eye drops can help.(for eye dryness).
3) If people are incontinent, care should be taken to keep the skin clean and dry. If the bladder is not functioning and urine is being retained, a tube (catheter) may be placed in the bladder to drain urine.
4) Physical therapy may also be used to prevent contractures and orthopedic deformities that would limit recovery for those patients who emerge from coma.

CNS Infections

(Dr.Khaled Hatem)

Central nervous system (CNS) infections are suggested by a constellation of signs, symptoms, and laboratory studies. The major groups of CNS infections include:

- Bacterial meningitis.
- Viral meningitis.
- Chronic meningitis.
- Acute encephalitis.
- Brain abscess.

HISTORY

The diagnosis of meningitis (inflammation of the meninges) is suggested when history includes fever, headache, and stiff neck.

- **Acute bacterial meningitis** :
  - is a neurologic emergency, with symptoms developing over hours or days.
  - Cerebrospinal fluid (CSF) studies show a neutrophilic pleocytosis, low glucose compared with blood glucose, and high protein.
  - Cultures or bacterial antigens are positive.
  - CSF pressure may be high.
  - Delay in diagnosis and treatment can lead to permanent injury or death.
- **Viral meningitis** :
  - is suggested by the constellation of fever, headache, and stiff neck-
  - the cerebrospinal fluid (CSF) features include a lymphocytic pleocytosis, normal sugar, and negative culture for bacteria.
- **Chronic meningitis** :

  - has a more indolent presentation,

  - may be associated with cranial nerve palsies, cognitive changes, or stroke-like events.

- The diagnosis of **encephalitis** (evidence of brain parenchymal involvement) is suggested when:

  - the history includes fever,
  - the acute onset of mental status changes (ranging from confusion to coma),
  - seizures, and
  - focal neurologic signs such as paralysis, acute psychosis, or aphasia.
  - CSF shows a lymphocytic pleocytosis with normal sugar.

- PCR for herpes simplex or other viral causes of encephalitis may be positive.
- MRI may show abnormalities in certain parts of the brain, such as the temporal lobe depending on the type of encephalitis.

- The diagnosis of **brain abscess** is suggested by:
  - subacute fever,
  - headache,
  - focal signs or
  - seizures,
  - signs of increased intracranial pressures.
  - Fever is seen in approximately 50% of adults and up to 80% of children with brain abscess.
  - Imaging shows a focal ring enhancing mass lesion or multiple lesions.
  - CSF studies should not be performed to avoid herniation due to mass effect.

Pursue the Following Points in the History:

- Has there been a recent respiratory or gastrointestinal infection?
- Has the patient had a recent infectious illness that may progress to meningitis (e.g., otitis media leading to pneumococcal meningitis)?
- Has the patient had a positive reaction to purified protein derivative, or known exposure to tuberculosis?
- Has the patient been exposed to others with infectious illness (e.g., meningococcus or Haemophilus influenzae)?
- Has there been recent travel to another state (e.g., exposure to mosquitoes causing arbovirus-associated encephalitis), or another country (cysticercosis in Central America)?
- Has there been a subtle personality change and low-grade fever (e.g., in chronic meningitis such as Cryptococcus)?
- What is the patient's occupation (e.g., painter exposed to Cryptococcus in pigeon droppings)?
- Does an underlying disease predispose the patient to CNS infection?
  - Lymphoma, leukemia.
  - Other malignancy.
  - Renal failure.
  - HIV/AIDS, other immunodeficiency states.
  - Alcoholism.
  - Diabetes.
  - Post-transplant patient.
  - Asplenic (functional or surgical).
- Is the patient receiving a drug(s) that predisposes to infection?
  - Chemotherapy.
  - Immunosuppressant or immunomodulator.
  - Corticosteroids.

- Has the patient had a recent illness such as mumps, or chickenpox that may be followed by meningitis or meningoencephalitis?

- Is the patient bacteremic, or has the patient recently been bacteremic? This increases the chances of secondary CNS infection.
- Has there been a recent head injury?
- Has there been a recent neurosurgical procedure or penetrating skull trauma?
- Has there been a recent insect bite leading to Lyme disease, or rickettsial infection, which mimics bacterial meningitis?

PHYSICAL AND NEUROLOGIC EXAMINATION

- Check vital signs. Temperature may be higher in bacterial than in viral CNS infection. Herpes simplex encephalitis often results in a high fever (104°F-105°F). Tachycardia is seen in bacterial and viral CNS infection.
- Check eardrums; examine sinuses for tenderness.
- Check for stiff neck. Look for Kernig sign (with thigh flexed on abdomen, patient resists knee extension), or Brudzinski sign (attempt to flex the neck, results in reflex flexion of the knee and hip). Remember that the elderly, infants, and immunosuppressed patients may have meningitis without prominent meningeal signs. Comatose patients may not have meningismus.
- Look for stigmata of chronic liver disease, and chronic lung disease as a predisposing factor for CNS infection.
- Look for peripheral signs of embolization in a patient suspected of having subacute bacterial endocarditis or staphylococcal septicemia.
- Examine the heart carefully (e.g., changing murmur in subacute bacterial endocarditis with valvular disease as source of septic embolism).
- Examine for lymph-node enlargement or splenomegaly. These signs may suggest a lymphoproliferative disorder, in which CNS infections commonly are seen.
- Is there evidence of CSF rhinorrhea caused by a defect or fracture in the cribriform plate?
- Examine for petechial or purpuric lesions caused by meningococcemia, or staphylococcal bacteremia.

LABORATORY

- All patients suspected of having meningitis should have a lumbar puncture (LP), and treatment with antibiotics as soon as possible
- . Record the opening pressure. If focal neurologic symptoms or signs are present and brain abscess is a consideration, obtain a contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) scan first, but do not allow significant delay when there is a high likelihood of meningitis. If meningitis is a reasonable possibility and imaging is necessary, it may be appropriate to give IV antibiotics immediately. Blood cultures should be drawn before antibiotics are begun. See Chapter 30 for a discussion of CSF examination.

  In addition, note the following points regarding meningitis and encephalitis:

- CSF pressure is usually moderately elevated in bacterial meningitis (200 to 300 mm H2O), and mildly elevated in viral meningitis or encephalitis.
- Cell count in untreated bacterial meningitis may range from 100 to 10,000/mm^3 with a predominance of neutrophils; the fluid is usually cloudy. In viral meningitis, cell counts of 10 to 1,000/mm^3 with a predominance of mononuclear cells are expected.
- CSF glucose is usually less than 40 mg/dL in bacterial or tuberculous meningitis (or less than 60% of simultaneously obtained blood glucose), whereas it is usually normal, or only modestly reduced in viral meningitis or encephalitis.
- CSF protein is usually higher than 100 mg/dL in bacterial meningitis, whereas a mild elevation (50-100 mg/dL) is expected in viral meningitis or encephalitis. A mild elevation also may be encountered in partially treated meningitis.
- Elevated CSF lactate levels are commonly encountered in patients with meningitis following neurosurgical procedures.

Gram stain usually detects the causative organism in bacterial meningitis. India ink stain is helpful in diagnosing cryptococcal meningitis, as are CSF and serum cryptococcal antigens. Bacterial antigens can be detected in the spinal fluid by a variety of special techniques and may be helpful if the patient received antibiotic therapy before the LP.

- Routine laboratory tests may offer clues. The white blood cell count is usually markedly elevated in bacterial meningitis and mildly elevated or normal in viral meningitis.
- Check for hyponatremia, caused by inappropriate antidiuretic hormone secretion, as a complicating feature in a meningitis patient with increasing lethargy.
- Chest radiograph may demonstrate a source of CNS infection (e.g., pneumonia or bronchiectasis).
- The electroencephalogram (EEG) may be normal or slightly slow in meningitis and encephalitis, but it often shows focal features in brain abscess and paroxysmal features in the temporal lobe in herpes simplex encephalitis.
- CT and MRI scans are usually normal in uncomplicated meningitis, but are often focally abnormal in herpes simplex encephalitis (temporal lobe). They may demonstrate complications of meningitis such as subdural fluid collections, hydrocephalus, or cerebral infarction.
- In patients with suspected viral CNS infections, obtain a serum specimen acutely, and save to compare with convalescent sera for an increase in antibody titers (e.g., in mumps infection).
- In suspected enterovirus CNS infection (Coxsackie, Echo), the virus often is detected in stool specimens. Mumps virus may be isolated from saliva, throat washings, or CSF.
- Bacteremia is present in many patients with bacterial meningitis and should be detected by appropriate blood cultures.
- Beware of coagulopathy in patients with fulminant meningitis (especially meningococcus).
- Use PCR (polymerase chain reaction) to identify herpes simplex.

- # TREATMENT

1)Bacterial Meningitis

- The mainstay of treatment of bacterial meningitis is intravenous antibiotics .
- For suspected undiagnosed bacterial meningitis in adults, start ceftriaxone 2 g intravenously (IV) every 12 hours.
- If penicillin-resistant pneumococcus is a concern, vancomycin 1 g IV every 12 hours should be administered, until susceptibilities are available.
- If Listeria is a consideration (immunosuppressed individual), ampicillin 2 g IV, every 4 hours should be added to the regimen.
- Appropriate dosing modifications for age and renal function need to be considered for all patients.
- For those with a severe allergy to beta-lactam antibiotics, chloramphenicol may be prescribed.
- Remember, if a lumbar puncture is delayed for any reason, consider giving empiric antibiotics before LP.
- Early treatment is crucial in these patients.

Other measures include the following:

- Seizures are common in meningitis, and usually are treated with intravenous phenytoin or fos-phenytoin.
- Fluid restriction to 1,200 to 1,500 mL/day may be needed to reduce brain swelling, or to control the syndrome of inappropriate antidiuretic hormone.
- Early use of dexamethasone 0.15 mg/kg IV every 6 hours for 2 days in children, and dexamethasone 10 mg IV q6h for 4 days in adults, may reduce unfavorable outcomes in adults and children with bacterial meningitis.
- Standard infection-control precautions (gloves, hand-washing, face/eye/mouth shield) and additional droplet precautions are essential for all cases of known or suspected meningitis.
- Family members, medical personnel, and others with close contact to patients with meningococcal meningitis should receive prophylaxis with one of the following regimens:
    - Ciprofloxacin 500-mg single oral dose (adults only).
    - Rifampin 600 mg orally every 12 hours for 2 days.
    - Ceftriaxone 250 mg intramuscularly (adult dosing; check for appropriate pediatric dosing).

2)Viral Meningitis/Encephalitis

- Treatment of viral meningitis is supportive.
- In cases of nonherpetic viral encephalitis, treatment is also supportive, and directed at possible complications.
- For herpes simplex encephalitis, acyclovir has greatly improved morbidity and mortality. Usual dosage is 10 mg/kg every 8 hours IV, with vigorous hydration to avoid nephrotoxicity.
- Take meticulous care to promptly and completely dispose of needles and syringes, and precautions should be undertaken in handling stool specimens in those with enteroviral infection.
- Isolate patients suspected of having measles, chickenpox, or rubella.

- Treat fever with acetaminophen or aspirin. A cooling blanket may be helpful for extreme hyperthermia.
- Treat seizures that accompany encephalitis.

3) CHRONIC MENINGITIS

Chronic meningitis presents with variable signs of meningeal irritation, cranial nerve dysfunction, and focal or global CNS dysfunction lasting 4 weeks or more. There is CSF pleocytosis, which may be caused by infectious or noninfectious processes (e.g., tuberculosis, fungus, hypersensitivity reaction, CNS tumor, chronic HIV, syphilis, and sarcoidosis). Treatment depends on the specific etiology.

4) BRAIN ABSCESS

If brain abscess is a consideration, avoid lumbar puncture until mass lesion has been excluded by CT or MRI. Aspiration or excision of brain abscesses, with appropriate antibiotic coverage and steroid therapy for edema, is the usual treatment. More conservative management of small abscesses with empiric antibiotics and close radiological follow-up is being used.

Muscle Diseases (Myopathies)

Dr.Rasha Elkapany

Definition:

Are diseases affecting voluntary muscles

Classifications:

Inherted

a. Muscular dystrophies.

b. Myotonic dystrophy.

c. Congenital myopathy.

d. Primary metabolic myopathy.

e. Congenital myasthenic syndrome.

f. Channelopathies.

Acquired

a. Inflammatory myopathy.

b. Drug and toxin induced.

c. Endocrinal.

d. Secondary metabolic.

e. Paraneoplastic.

f. Myasthenia Gravis and Eaton Lombert.

Clinical presentations:

1. Wealcness:
    - Most important.
    - Bilateral, symmetacil iproxima;.

2. Muscle wasting or hypertrophy in some cases.

3. Fatigre and exercise intolerance.

4. Pain: either focalized due to trauma or ischemia or generalized due to inflammation or drug induced.

5. Muscle cramps.

6. Myoglobinuria passage of dolce urine due to extensine muscle damage.

Investigations:

1. serum enzymes: creatine kinase level is elevated.
2. EMG:- (electromyography)
    - amplitude and duration of motor unit potentials with polyphasicity.
    - complete interference pattern.
3. Muscle biobsy.
4. Molecular genetic studies.

Muscular dystrophies

Def:

Are primary inherted degenerative progressive disorders of muscle.

The main site of pathology is muscle fiber membrare.

Classification:

Autosomal-Recessiue	**Autosomal – dominant**	**Linked**
Limb girdle congenital ditaltype.	Fascioscopubumeral oculopharyngeal Distal myopathy limbgirdle (uncommon)	Duchene becker

Duchene muscular dystrophy

- X- linked affect boys
- Age of onset: first decade of life.

  (usually at age of walky, sometimes can lead to delayed walky)

- **<u>Clinical picture:</u>**

1. Weakness:
    - start in pelvic girdle muscles.
    - Lead to difficulty in climbing stairs.
    - Child raises from floor in a characteristic fashion(Gower's) waddling gait.
    - Shoulder girdle affection within 2-3y.
    - Ambulation is lost at about 10 years.

2. Muscle hypertrophy:

- In early stage.
- Most evident in calfmuscles quadriceps muscle.

3. Exaggerated lumbor lordosis prootuderant abdomen.

4. spinal deformity and contractures.

5. Respiratory muscle weaknes recusant chest infections.

6. cardiac involvement charactenistic EGC changes (tall rwaves right pericardial leads narrow Q waves in lelt pericardial leads)

7. Delayed speech, low IQ.

Management:-

- Steroids in low dose slows progression of the disease.
- Gene therapy.
- Regular physical exercise.
- Splinting and walking aids.
- Spinal orthosis.
- Occupational therapy.
- Dietary advice to avoid obesity.
- Assisted verntillation if Reap n. Affection.

Becker Muscular dystrophy

Benign type:

Age: second – to third decade of life.

C/ P:-

- Weakness in pelvic girdle and shoulder girdle.
- Exercise induced muscle cramps and calf hypertrophy(early)

- No cardiac involvement, rontracture or deformity.

Limb girdle muscular dystrophy

Age: 2nd to third decade.

Both sex.

C/P:

- Either shoulder girdle addiction first in soy.
- More benign from.
- Pelvic girdle start first.
- Contractures and skeletal deformities are late.

Fascia scapula humeral

AD.

Age: Second decade of life.

C/P:

- weaknes involue facial muscles.
- Shoulder girdle.
- Anterior tibial muscle.
- Abortive cases occus.

Oculopharynged muscular dystrophy

Age: 5^{th}-6^{th} decade.

C/ P:

- Ptosis.
- Dysphasia.
- Facial weakness.
- Limb girdle- Late.

Distal type of myopathy

Age: 40-60tears.

Sex: male more.

C/P:

- Weakness of small muscles of hand.
- Anterior t. bial muscles.

Myotonic dystrophy

- AD
- Age on onset : adolescence
- Sex : make more
- CIP

a) – weakness and wasting of : * Facial muscles and muscles of mastication

* slernomastoid muscle

* in the limbs > distol

b) myotonic phenomenon :- * resp muscles > recruyent

* delayed relaxation after muscle contraction either voluntorly or mechanical.

* affect tongue muscles of hard – difficulty relaxing hrip

Jaw > difficult cheering

- with repeated contraction (worm up phenomnor)
- extramuscular manifestations;

heart > conduction defect

eye > Gtaract

endocrinal > testicular atrophy , infertility frontal baldness

CNS > mental retordation.

Diagnosis : DNA aralysis

Management : Genetic counseling

Regular ECG :- in conduction block > pacemaker

Treatment of chest infection

Treatment of cataract

Myotonia Congenita

- AR
- Age : first and second decode
- Sex : female more
- CIP :
- Generalized myotonia decrease with exercise and warm and increase by rest and cold
- Hypertrophy of the muscles
- Transient weakness of muscles

Diagnosis : EMG

DNA analysis

Treatment mexilitire

Paramyotonia congenital

Myotonia precipitated and increased by execcise and cold.

Periodic por-lysis

Primary hypolcalemic **primary hyperlcalemic**

* attacks fgeneralized weakness paring bulbor and resp.

* preapating factors :

Carbohydrates diet cold , fasting , rest , emotional stress

Emotioned upset

* treatment

- avoid precipitation factors

- oral potassium chloride - lowdase

- acetozolamide - thicizide

- acetozolamide - inhalation y B-stimulant

Inflammatory myopathy

Def : Diseases characterized by presence of inflammatory infiltrate within muscle.

Classifications:

- Idiopathic : Dermatoryositiss pohmyasits , inclusion body myositis
- Infective * associated with collagen disease

Idiopathic inflammatory myopathy

CIP : of dermatomyosits and polymyositis

Age : 5-14 years in dermato

50-60 years in poymyoscls

Onset : subacute in dermatomyasils

Gradul in polymyases

Rash – in 90 % Y dermatomyosils affect face , extensor suface f faints

erythmatus , photosensite

Weakness – proximal in upper limb , lower limb

Neck muscles

Bulbar , muscles

* Painful , tender , swollen muscle in dermatonyostis

* extramuscular manifestation

e.g: Paynaud disease arthralgia

* malignancy in 20 y. of deimatomyositis

Diagnosis :

- laboratory : * Elevation of ESR , CRP

* CK

* Cirulating antibodies

- EMG
- Mescle biobsy

Treatment :

1) prednisilone : 1mg/kg body weight
2) immunosuppressive drugs : azathioprire
3) intravenous immunoloblin

poor prognosibe factors : old age , time of instiation of treatment , extcamuscular manifestation

Indusion body myoscls

- age -0 > so years old
- males

CIP : early , weakness F quadriceps, muscle finge flexors

Late : dygsphogio

Diagnosis > muscles biobsy

Treatment > immunospreastise drugs , ineffective

Disorders Of The

Neurmoucular Ganction

Dr.Rasha Elkapany

Definition : > clinical condition : related to dysfunction at neuromuscular junction :

1- myasthenia Gravis

2- lambert eaten

3- congenital myasthenic syndrome

4- acquired neuromyotonia C Iscac`s syndrome

each is related 10 disturbedion channel function

Myasthenia Gaus

- Autoimmune disease with production of antibodies against acety \ choline receplor of neuromuscular function leading to destruction
- CIP
- Age : 20-40 years (females > 20-24 years)

  (males > 30-34 years)
- Sex : female more
- Easy fatiguability espiceally on repetition of movement
- Weakness of :

- Ocular muscles >> ptosis, ophthalmoploie diplopia

  Presenting symptom in 90 %

  If no spread of weakness more then 2 years >> pure oocular nyasthenia.

- facial muscles cetractors of argle fmouth
- bulbar muscles >> dysphogia and dysorthn
- nesck muscles >> extensors
- limb muscles : roximal more in UL > LL
- respiratory muscles :
  - weakness varies durig >> coorse of the day

    activity

    emotions

    menestrvation

    infection
  - incidence of other autoimmune diseases

Diagnosis :

1- Clinical tests :

a) induction of fatigue >> maintain upward gaze >> pasis count from 1-50 >> dysorthria

b) walker`s test

- sphygmomanometer is applied toarm and raise pressure above systolic
- the patient is asked to perform motor activity
- relase the sphygmomanometer - ptosis

c) phormacobgiccal tests

- prostigmine test : injection of 215 mg prostigmine + one ampoule atropine

  >>> improvement of ptosis within 10-30 minutes in myaestheria

- tensilon test : Edrophonivm infection intravenous in proveent F ptasis within 2 minutes

- Serological : -

☒ Anti-acety\ choline receptor antibody : +ve in 90% of generalized myastheir and 50 % of ocular myasthenia

☒ Antinuclear Ab. And thyroid functions

- Radiobgy : X-ray – CT chest to bletect

- Electromyography: repititviere supramax imcl stimulation

Decremental response 710 %

* single fibre EMG

- Treatment :

There are various sterategies used for treatment of myasthenia Gavis :

a) acety\ cholinesterase inhibitors

b) immunosuppressive agents

c) plasma exchange

d) thymectomy

the regimen depend on : age of the patient ,

presence or absence of enlorged thymus

concurrent medical problems

1- Acety\ cholinesterase inhibitors

- phridostigmine : 30 – 60 mg every 5 hours
- neostigmine

2- Corticost eriods : indication :

- Generalized myasthenia above 50 years
- Pure ocular myasthenia
- If acely\cholire receplor AB is ve
- If no response to ant : cholinest erese drugs

* prednisilone 1.5 mg/ kg

3- Immunosuppressive drugs – azathioprire , methotraxate

If contraindication 10 steroid.

4- Thymectomy : indications :

* presence of thymomy

* Generalized myasthenia < 50 years

* acety\ cholin receptor AB the lead to remission in 1/3 y cases

5- Intravenous immunoglobulin , pasma excharge :

- both equal in ellicacy
- indications : in myasthenic crisis
- prior to thmectomy

Myasthenic Crisis :

- Should be differentiated from cholinergic crises by tensilon test
- Ph should be in ICU
- Monitoring pulmonary functions
- Intubation and mechanical ventilation
- Plasma exchange or Iv . Iy.
- Plus steroioy

Lambert Eaton

- Presynaptic disorder
- Ab against Ca channel >> reluse F Ach
- 50% associated with lung cancer
- Clinical picture
- Weakness of lower limb >> gait disturbance
- Mild ptosis
- Autonomic F eatures : impotence and dry mouth

Diagnosis :

Serological >> antibodies again ca channel

- EMG >> murked >> compound action potential repitive stimulation : increamental response
- Treatment :> Acety\ cholinesterase inhibitors >> variable response

3/4 diaminopyridine >> delay >> repotarization