Brain Tumors in Practice

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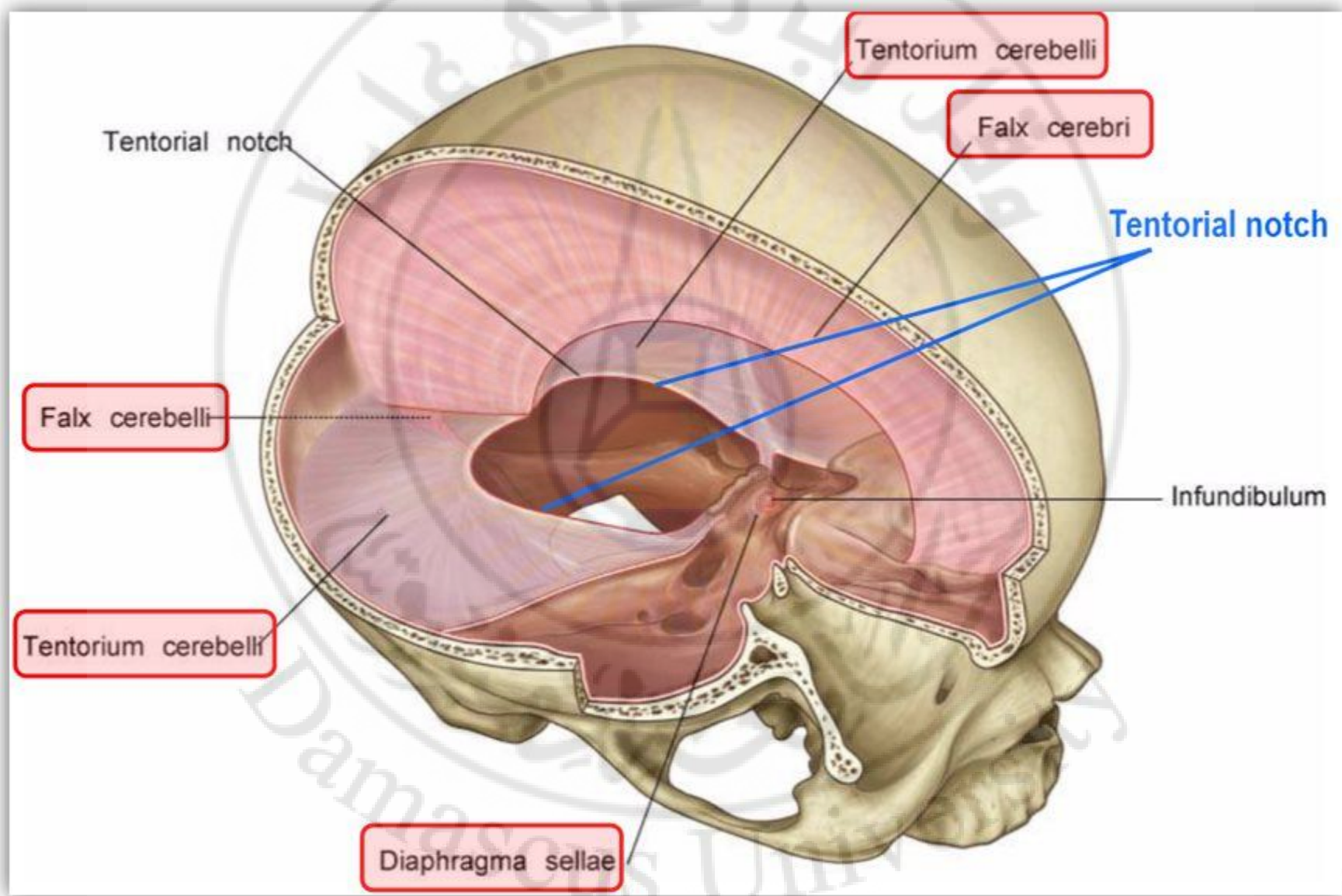
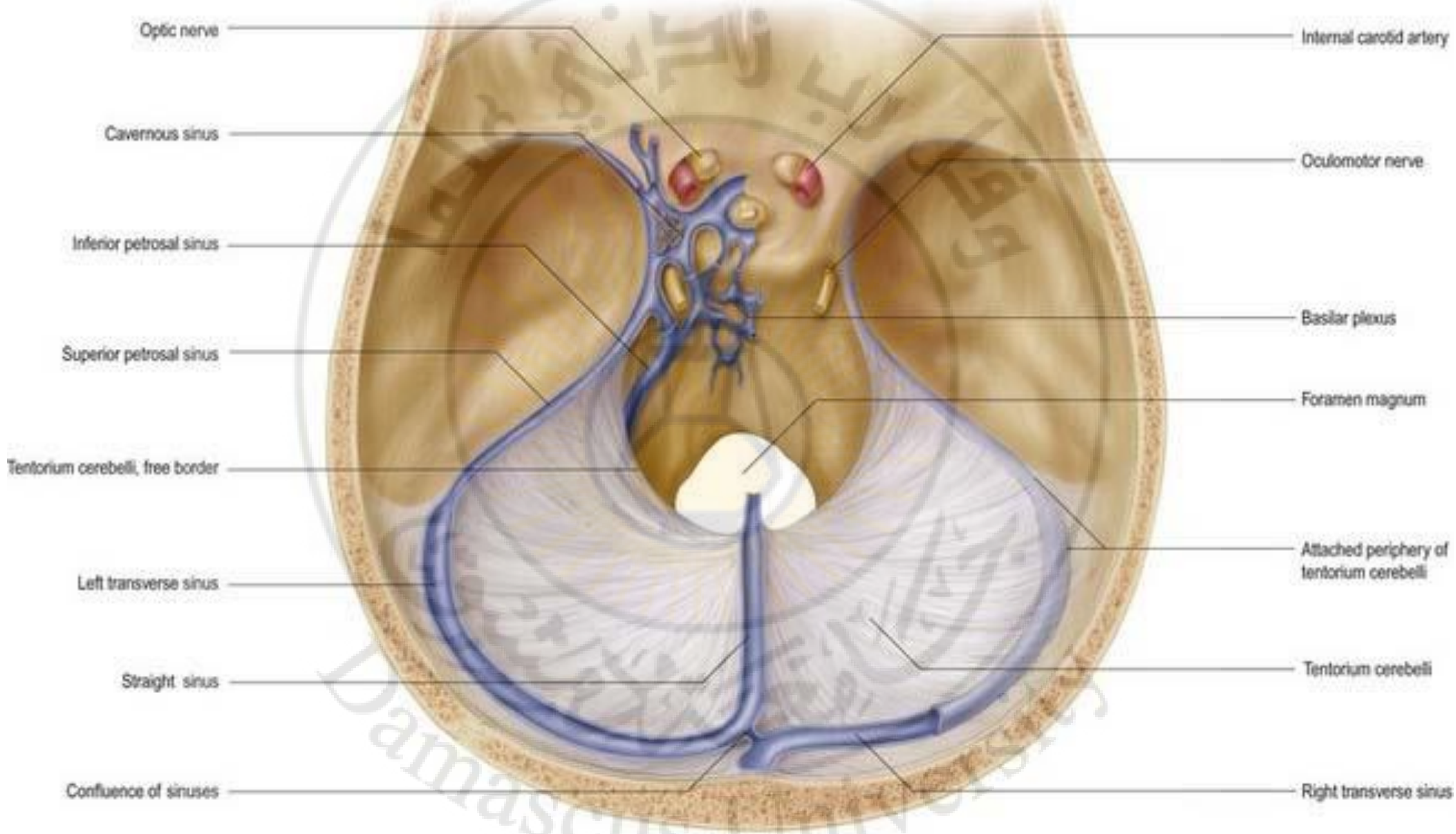
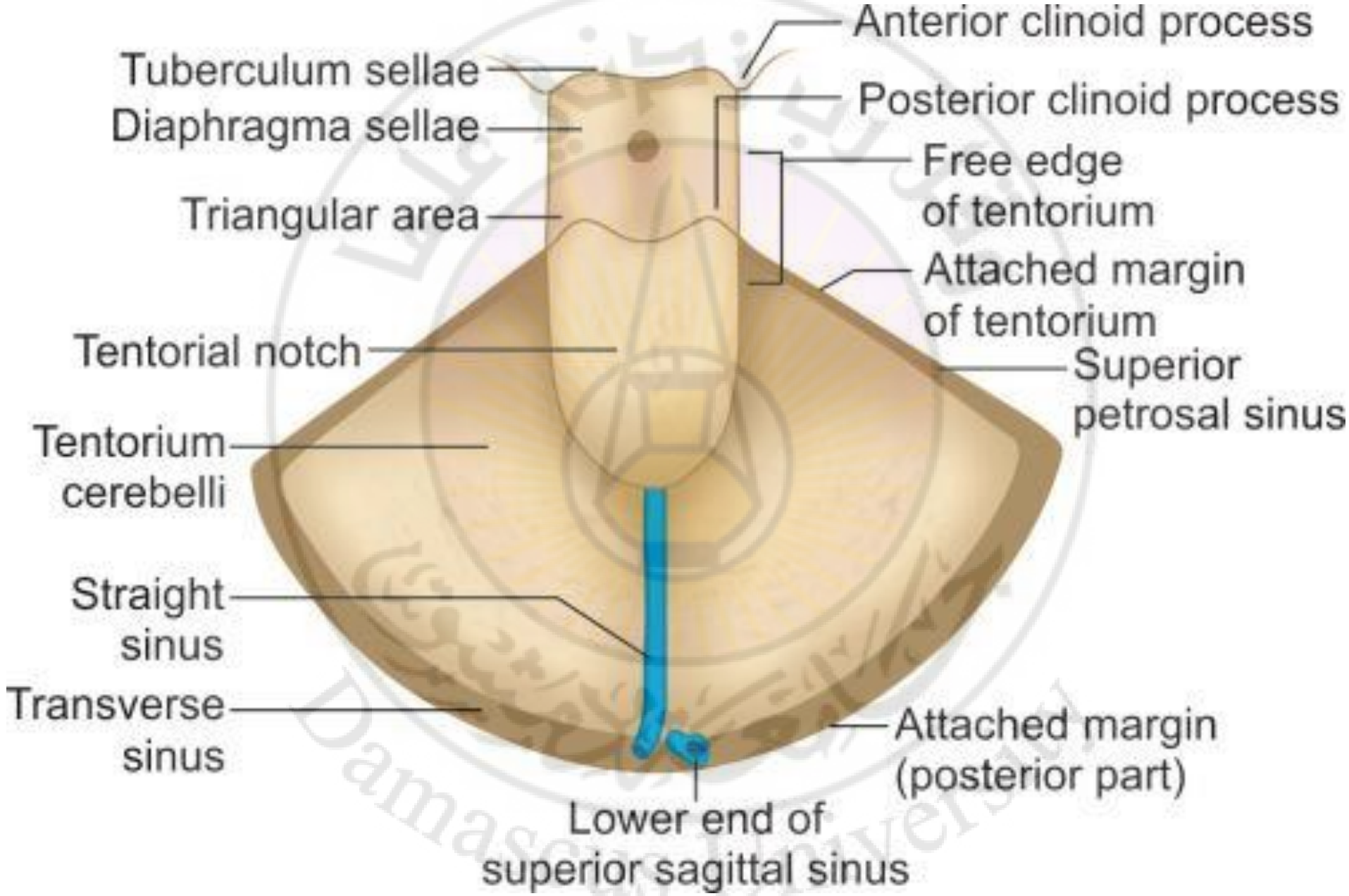
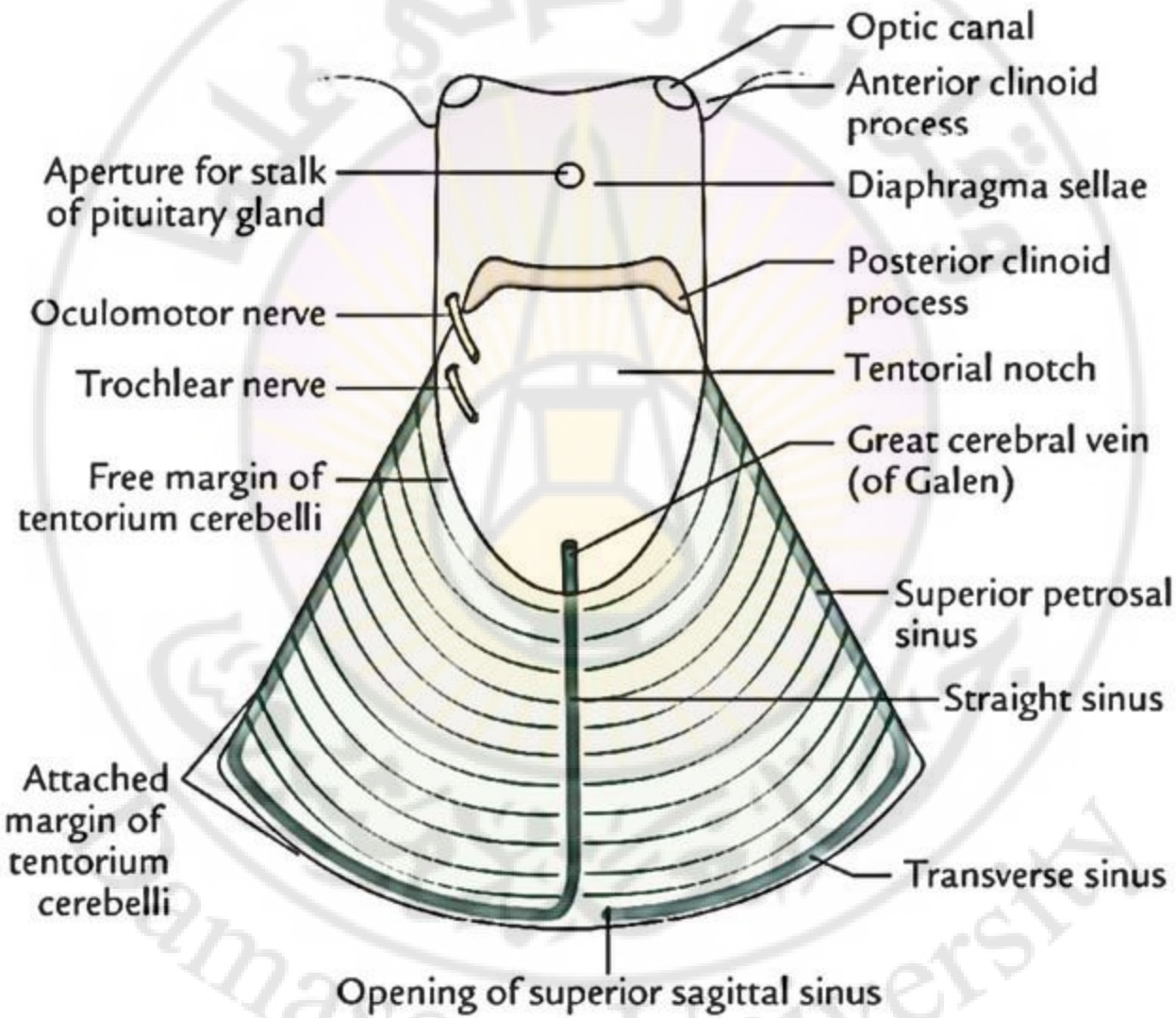
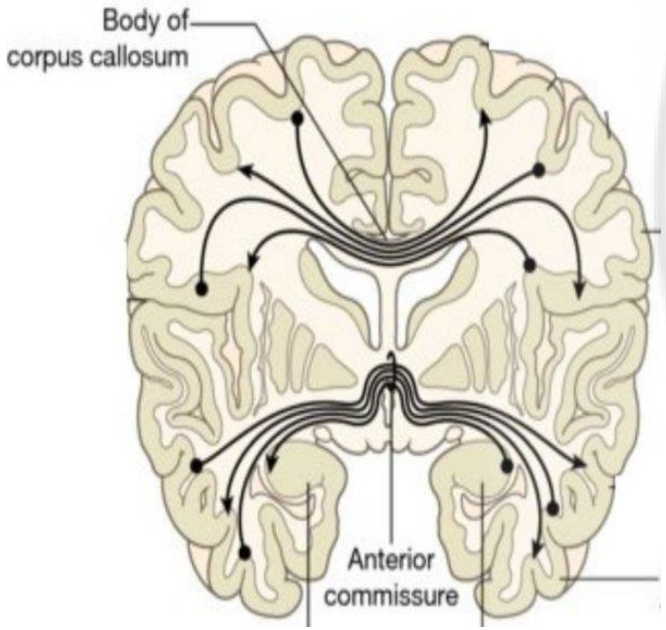
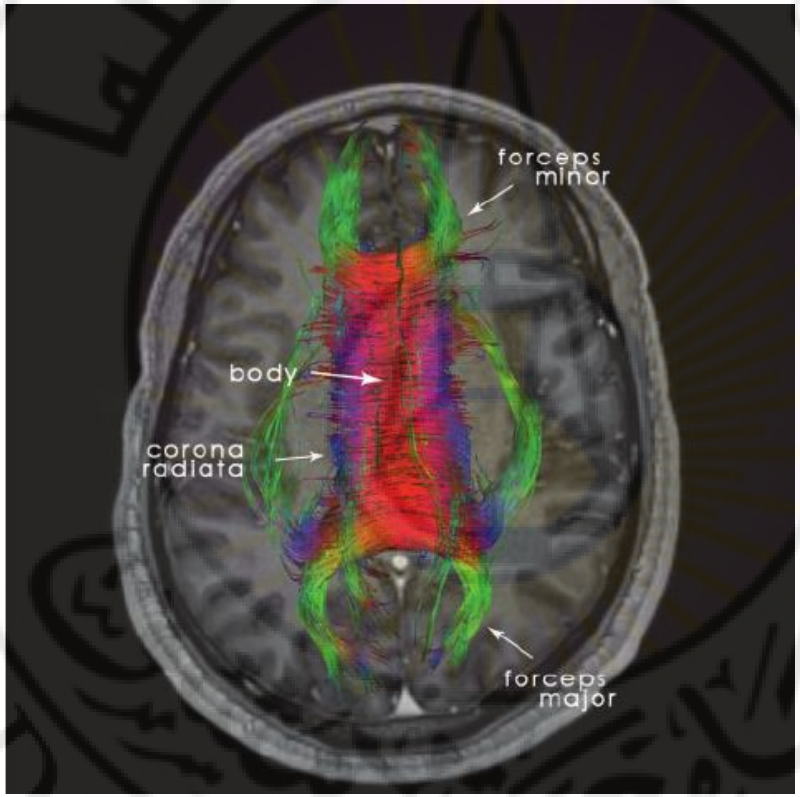

Tentorium cerebelli
Falx cerebri
Tentorial notch
Tentorial notch
Falx cerebelli
Infundibulum
Tentorium cerebelli
Diaphragma sellae

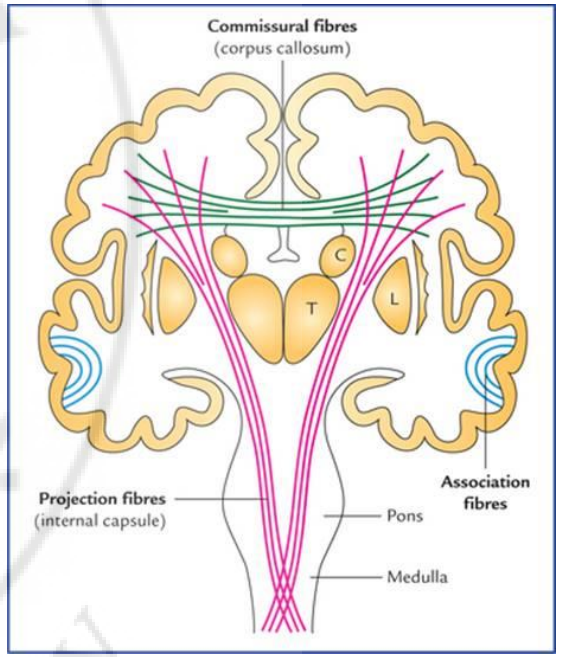

Optic nerve
Cavernous sinus
Inferior petrosal sinus
Superior petrosal sinus
Tentorium cerebelli, free border
Left transverse sinus
Straight sinus
Confluence of sinuses
Internal carotid artery
Oculomotor nerve
Basilar plexus
Foramen magnum
Attached periphery of tentorium cerebelli
Tentorium cerebelli
Right transverse sinus


Anterior clinoid process
Tuberculum sellae
Posterior clinoid process
Diaphragma sellae
Free edge
of tentorium
Triangular area
Attached margin
of tentorium
Tentorial notch
Superior
petrosal sinus
Tentorium
cerebelli
Straight
sinus
Transverse
sinus
Attached margin
(posterior part)
Lower end of
superior sagittal sinus

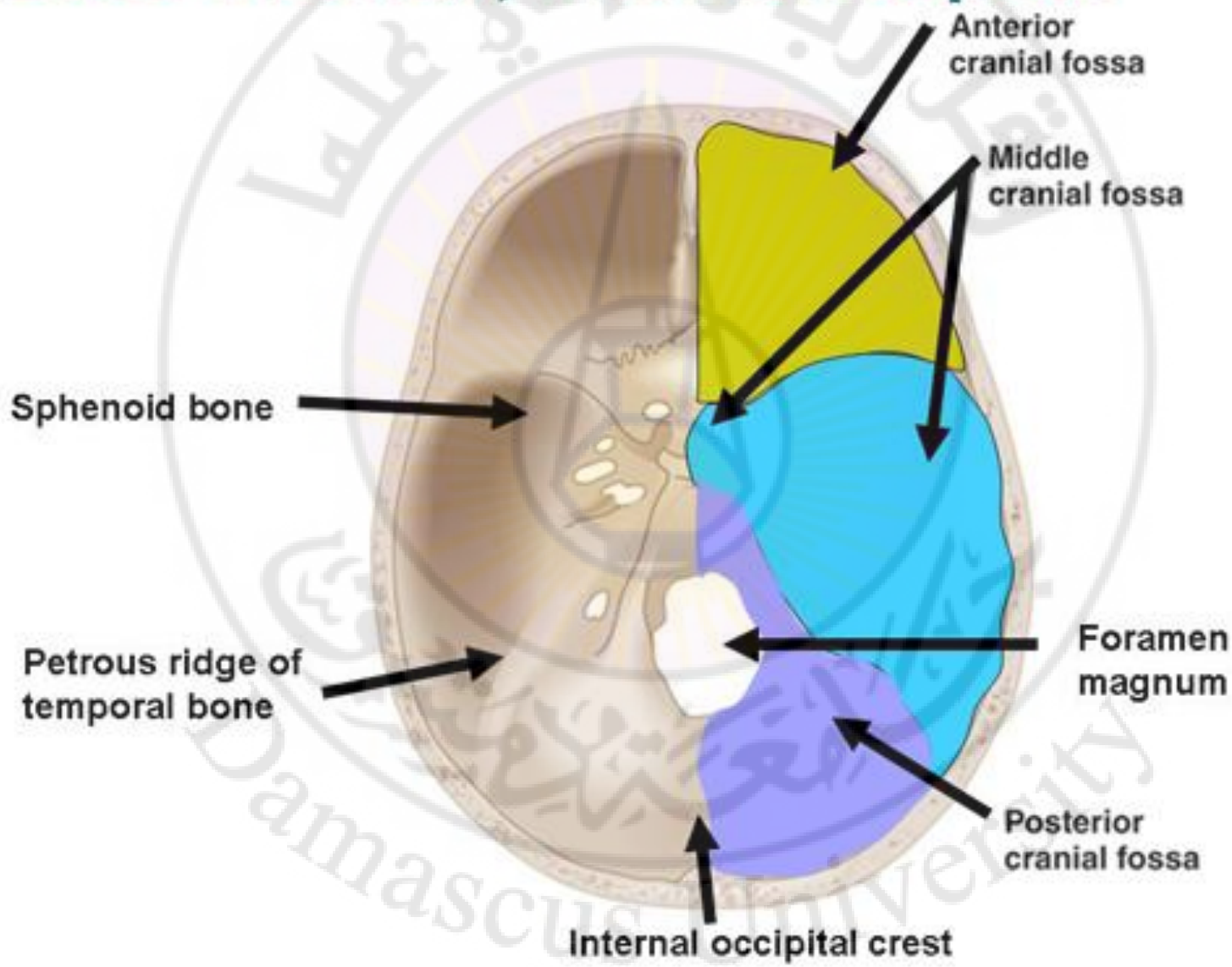

Optic canal
Anterior clinoid process
Aperture for stalk of pituitary gland
Diaphragma sellae
Posterior clinoid process
Oculomotor nerve
Trochlear nerve
Tentorial notch
Great cerebral vein (of Galen)
Free margin of tentorium cerebelli
Superior petrosal sinus
Straight sinus
Attached margin of tentorium cerebelli
Transverse sinus
Opening of superior sagittal sinus







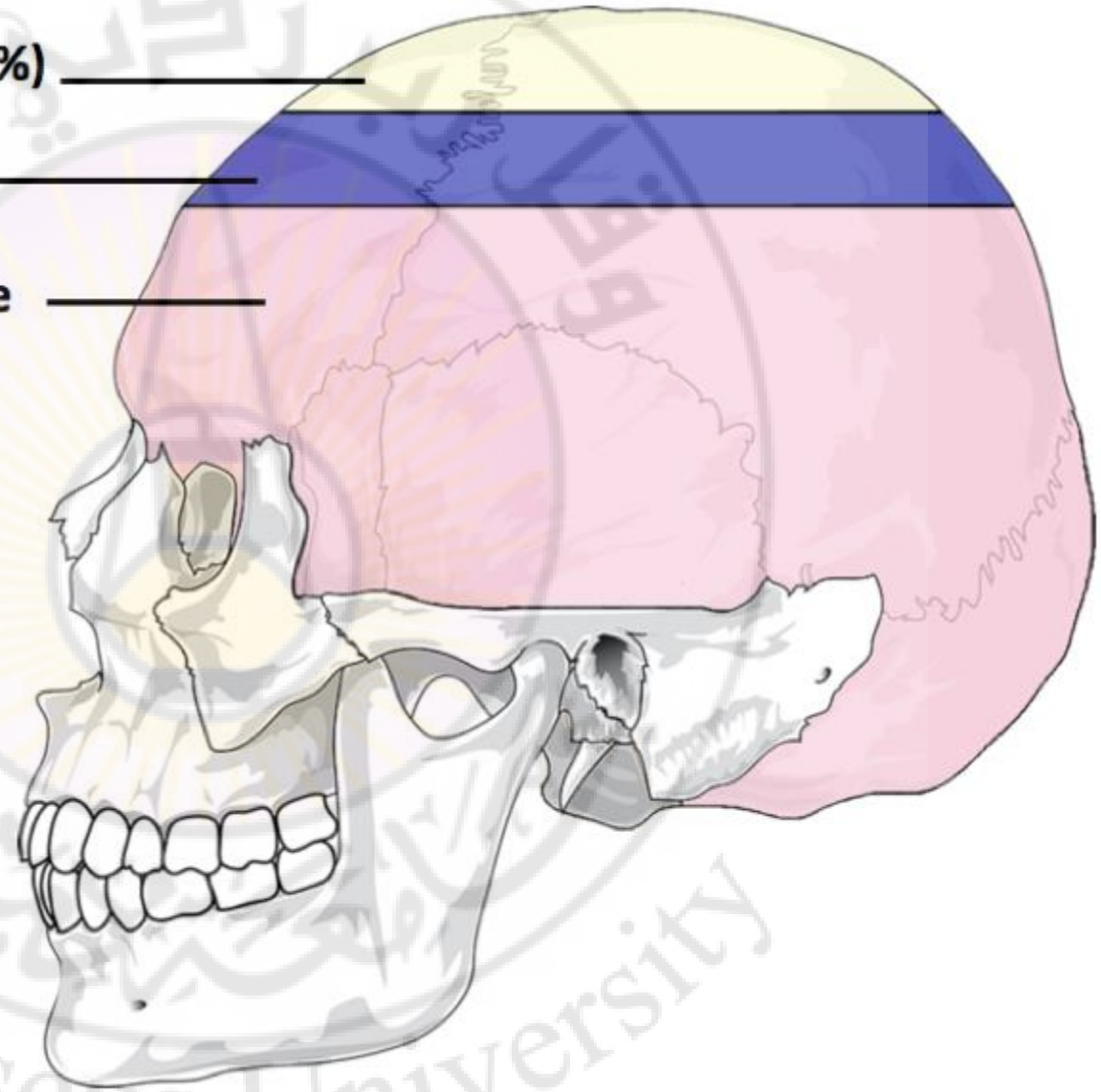
Base of Skull, Internal Aspect



CSF volume = 150ml (10%)

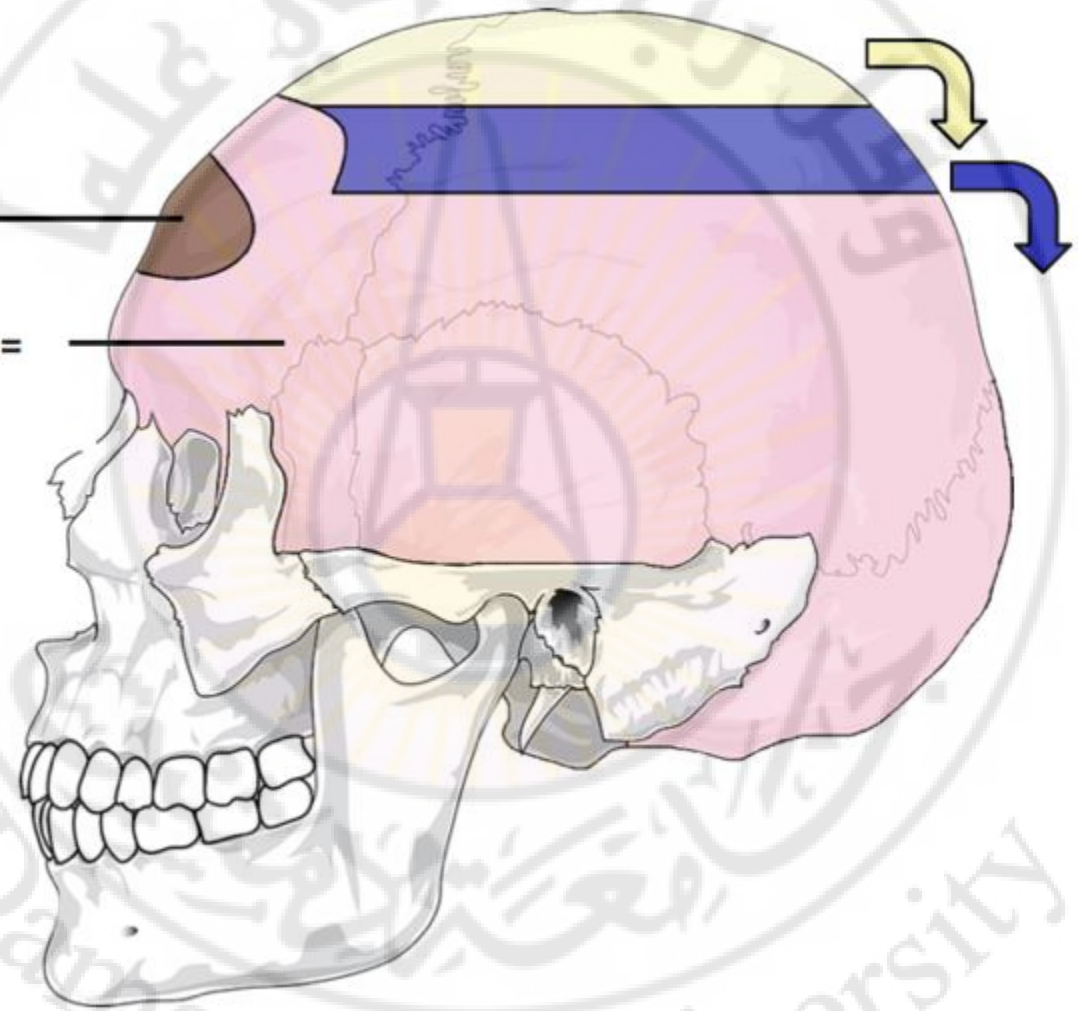
Blood volume = 150ml (10%)

Brain parenchyma volume
= 1400ml (80%)

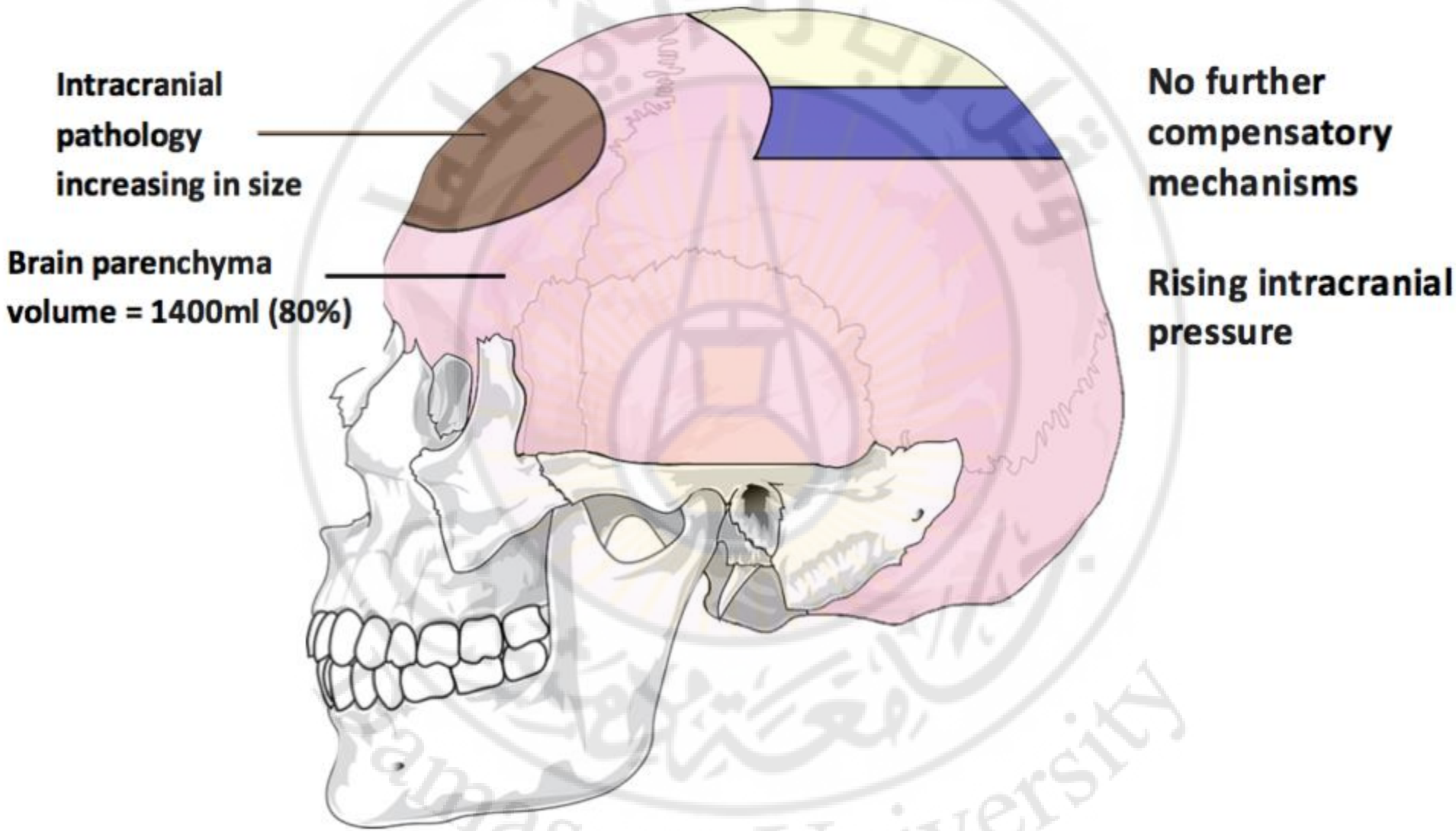


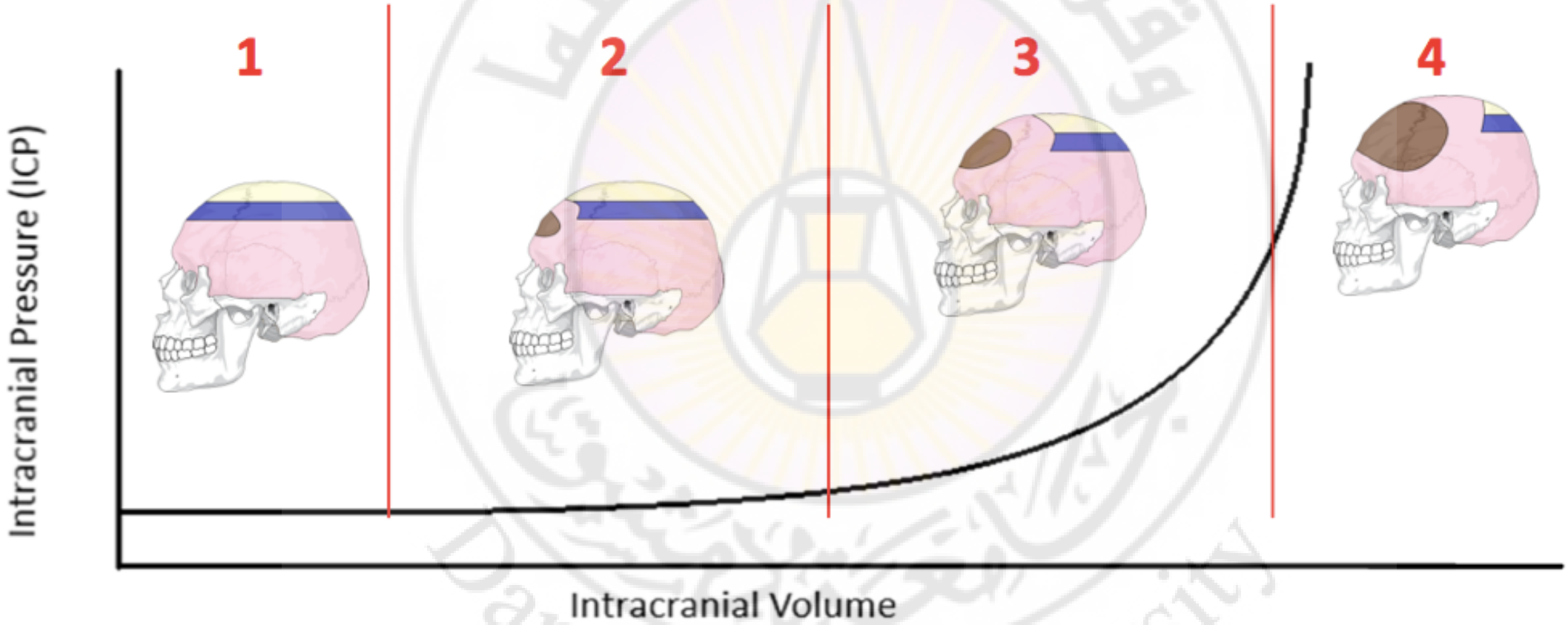
Intracranial pathology,
e.g. tumour,
haemorrhage etc.

Brain parenchyma volume =
1400ml (80%)

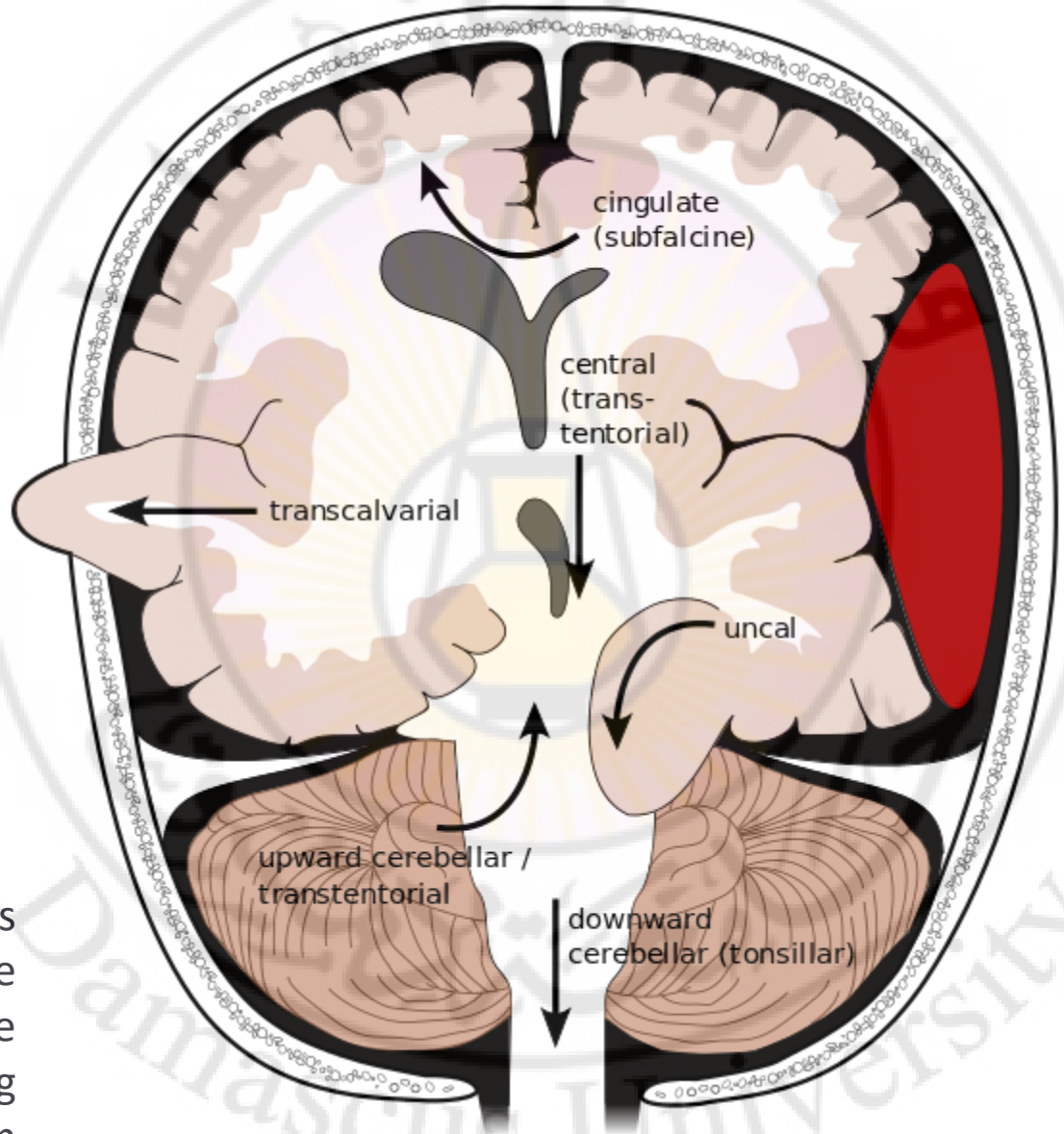


Compensation:
↑ CSF drainage via ventricular system
↑ Venous drainage via dural venous sinuses


Intracranial pathology increasing in size
Brain parenchyma volume = 1400ml (80%)
No further compensatory mechanisms
Rising intracranial pressure


1
2
3
4
Intracranial Pressure (ICP)
Intracranial Volume

Herniation

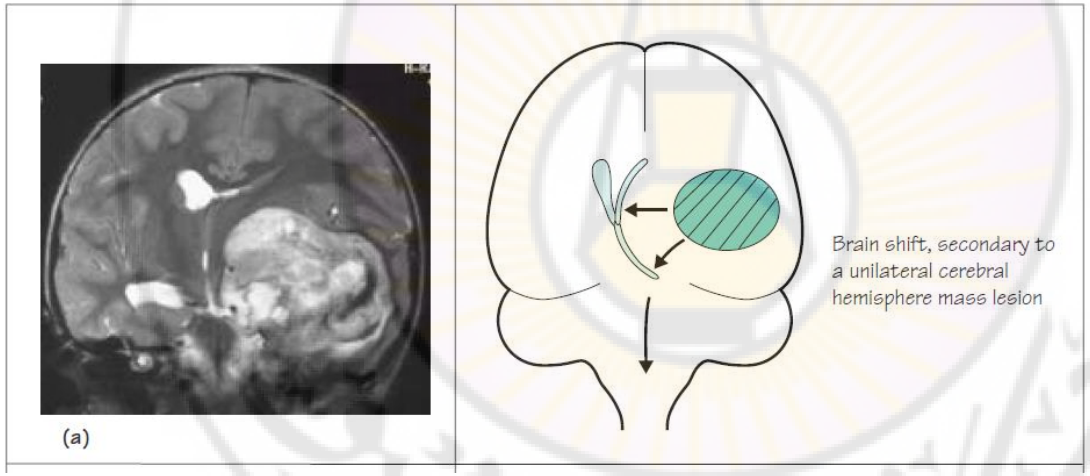


•**Uncal herniation** refers to displacement of the medial part of the temporal lobe (uncus) below the tentorium cerebelli

•**Tonsillar herniation** occurs when the cerebellar tonsils are forced downwards through the foramen magnum, causing compression on the brainstem (fatal if left untreated)

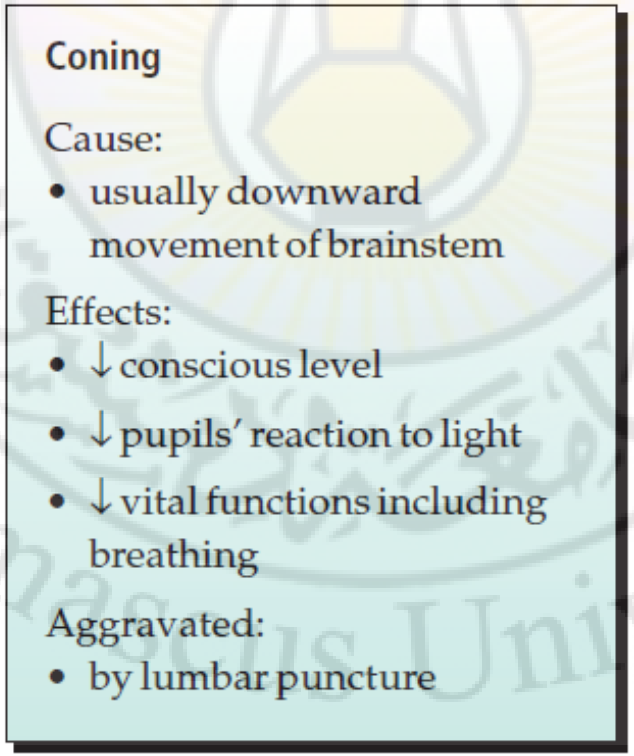
When a mass lesion is making one cerebral hemisphere too large for its compartment:

- the supratentorial midline structures (corpus callosum and 3rd ventricle) are pushed towards the opposite side of the skull below the falx;
- the infero-medial part of the cerebral hemisphere is pushed through the tentorial hiatus (compressing the midbrain);
- the whole brainstem is pushed downwards so that the lowermost parts of the cerebellum and medulla oblongata become impacted in the foramen magnum.

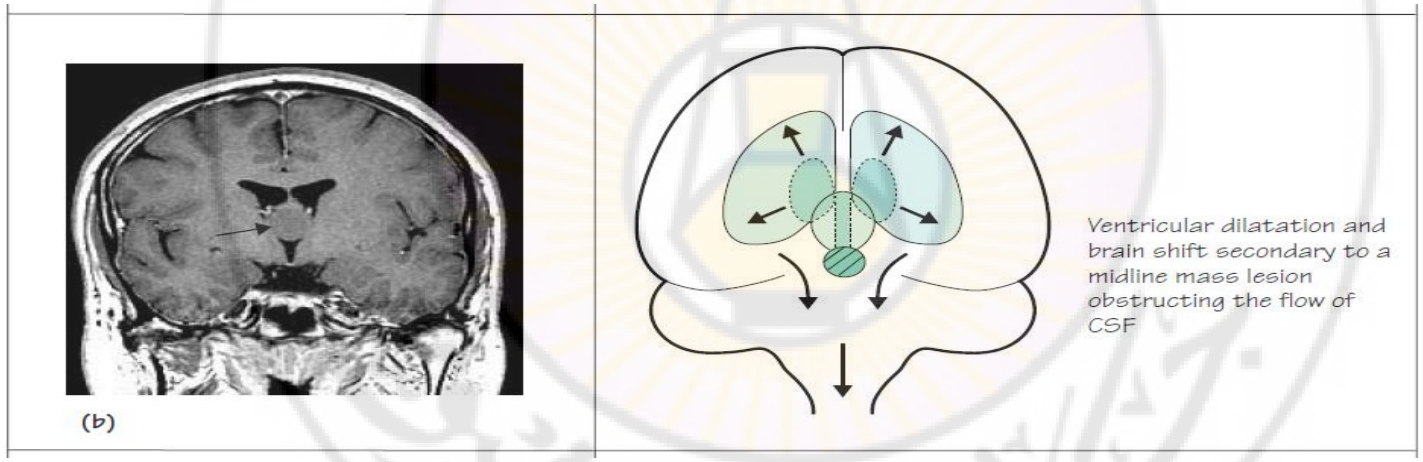


(a) Brain shift secondary to a unilateral cerebral hemisphere mass lesion.

The movement at the tentorial hiatus is known as *tentorial herniation*, and the impaction at the foramen magnum is known as *coning of the medulla*. They commonly occur simultaneously.
The effects on the patient are:
• depression in conscious level (distortion of the reticular formation lying throughout the whole of the brainstem);
• an impairment of ipsilateral 3rd nerve function and dilatation of the pupil (tentorial herniation compressing the midbrain);
• interference with the vital functions of respiration and circulation (compression of the medulla oblongata).

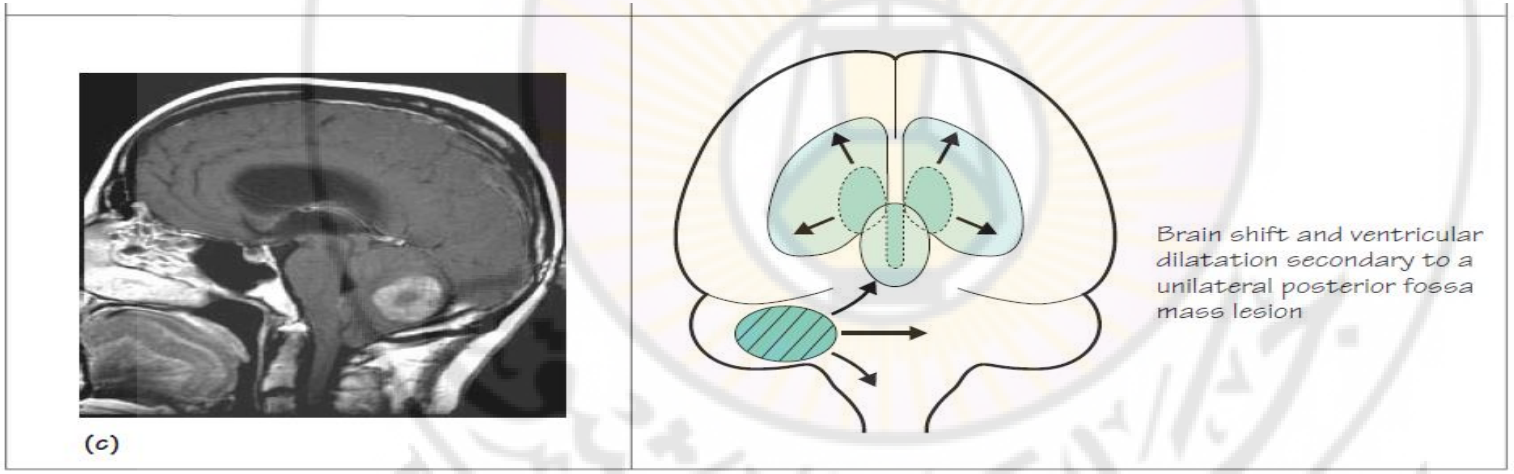


A mass lesion situated in the midline causes obstruction to the downward flow of CSF through the ventricular system. Under such circumstances, the ventricles above the site of obstruction dilate, and both cerebral hemispheres become too large for their compartments. Bilateral tentorial herniation and coning are likely to occur with the same dangerous clinical consequences.



(b) Ventricular dilatation and brain shift secondary to a midline mass lesion obstructing the flow of CSF.

In the presence of a unilateral posterior fossa mass lesion, there is movement of the midline posterior fossa structures to one side. This may compress the 4th ventricle sufficiently to block the downward flow of CSF, resulting in ventricular dilatation above the site of obstruction. There will be downward movement and compression at the level of the foramen magnum. At the tentorium cerebelli, there may be upward movement and compression of the midbrain or, if the supratentorial ventricular dilatation becomes very marked there may be downward herniation bilaterally. Depression of conscious level, dilated pupils and impaired vital functions may all result from such a lesion.

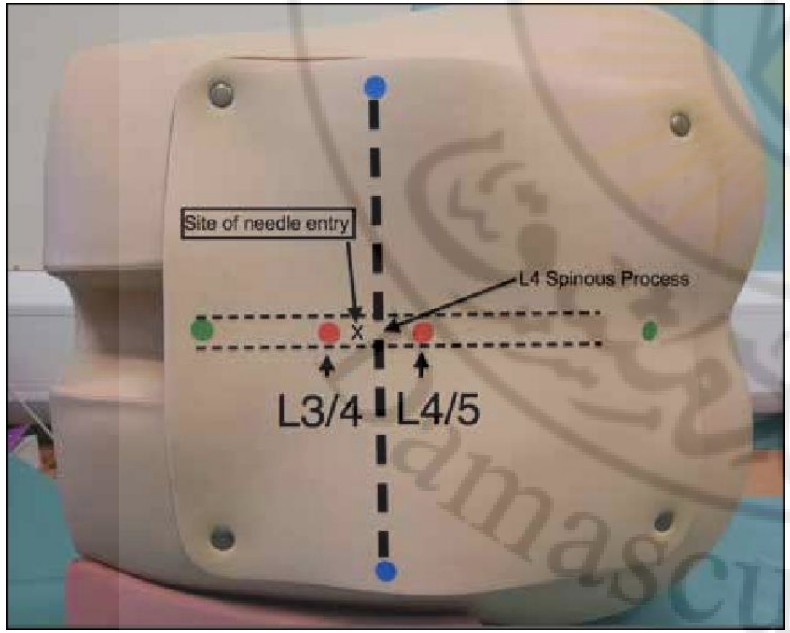


(c) Brain shift and ventricular dilatation secondary to a unilateral posterior fossa mass lesion.

Lethal lumbar puncture

Lumbar puncture is dangerous if intracranial pressure is raised due to a mass lesion. It reduces the CSF pressure below the foramen magnum. This can encourage downward brain shifts with tentorial herniation and coning of the medulla.

On the other hand, where headache and papilloedema are due to a general elevation of intracranial pressure without any mass lesion, e.g. in BIH, in meningitis and uncomplicated subarachnoid haemorrhage, lumbar puncture is safe and may relieve symptoms.



Practical tip

1. Always measure the CSF pressure at the start of a lumbar puncture
2. Make sure the patient is relaxed and not too tightly curled
3. If the pressure is unexpectedly elevated (>25 cm of CSF):

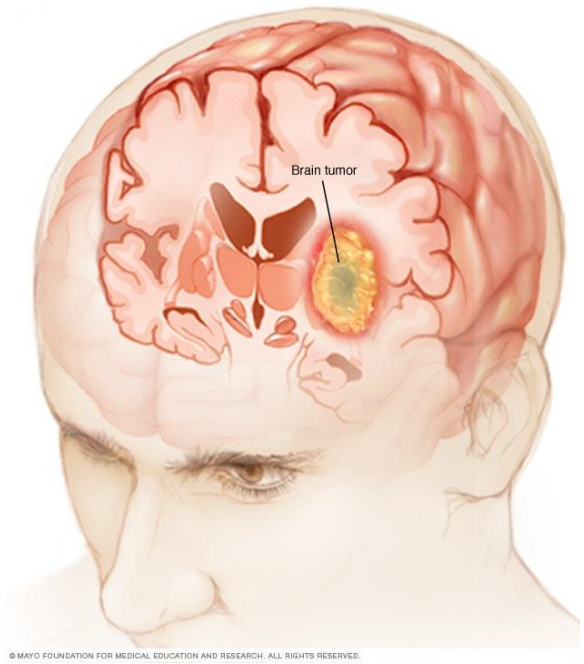
- collect the sample in the manometer
- take out the LP needle
- secure IV access in case you need to give mannitol
- start neurological observations at 15-minute intervals
- arrange an urgent brain scan
- consider obtaining neurosurgical advice

False localizing signs

False localizing sings

- Sixth nerve palsy
- 'Frontal' signs
- Impaired up-gaze
- Signs of coning

Clinical features



Clinical features of brain tumours

- Raised intracranial pressure
- Epilepsy
- Evolving neurological deficit

Raised intracranial pressure

The cardinal features of raised intracranial pressure are:

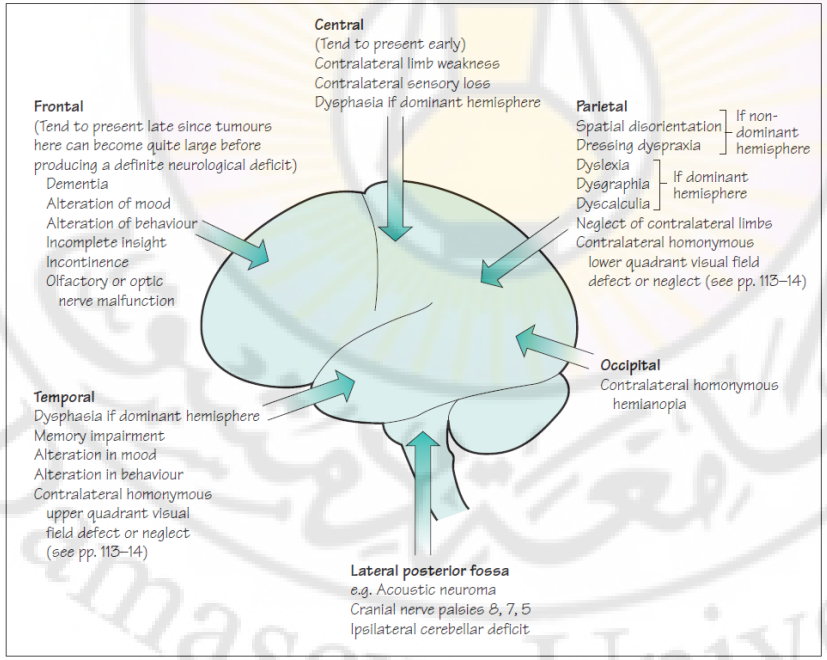
- headache;
- vomiting;
- papilledema;
- false localizing signs;
- depression of conscious level;
- signs of tentorial herniation and coning.

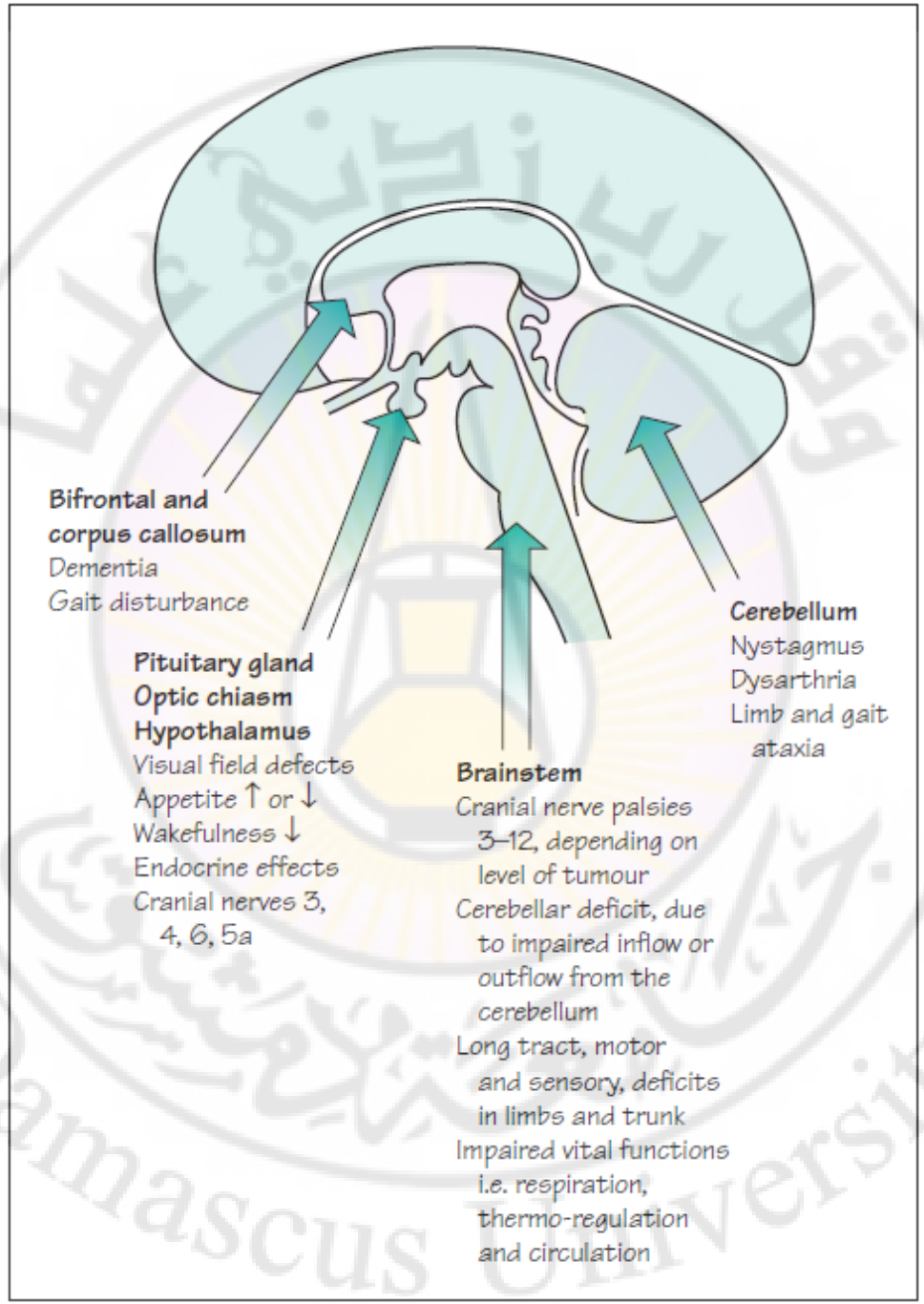
Epilepsy

Focal epilepsy, focal epilepsy progressing on to a generalized tonic–clonic seizure, tonic–clonic seizures with post-ictal focal neurological signs, and tonic–clonic epilepsy without any apparent focal features may all indicate the presence of a tumour in the cerebrum. (Focal epilepsy is discussed in detail on pp. 196–8). Epilepsy is not a feature of posterior fossa tumours. Epilepsy is not commonly caused by tumours, and less than 50% of cerebral tumours produce epilepsy, but the occurrence of epilepsy in adult life should prompt the possibility of a brain tumour in the doctor's mind.

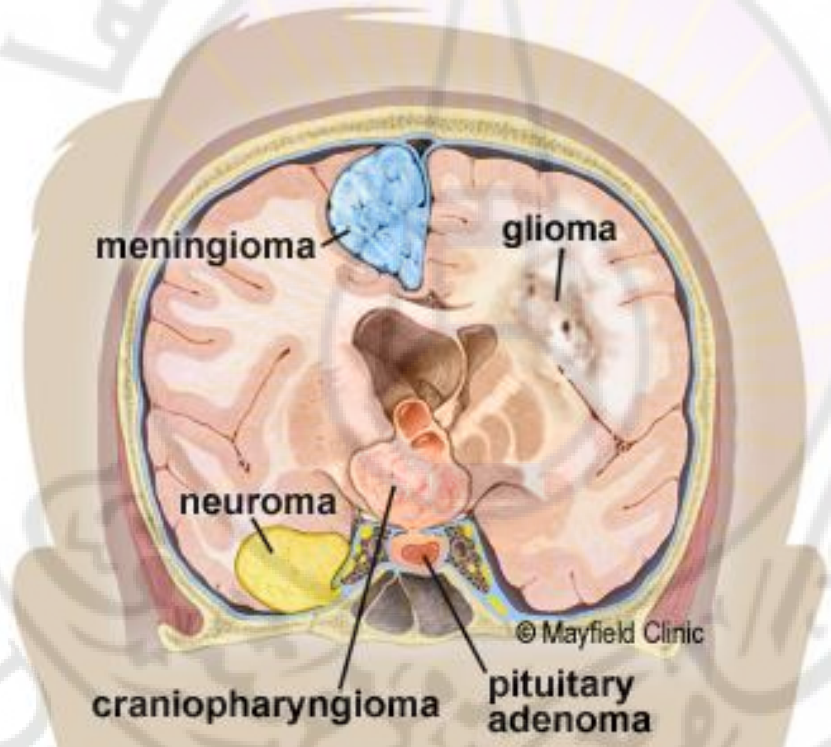
An evolving focal neurological deficit

The presence of a tumour impairs the function of the part of the brain in which it resides. The nature of the evolving focal neurological deficit clearly depends on the site of the lesion




Bifrontal and corpus callosum
Dementia
Gait disturbance
Pituitary gland
Optic chiasm
Hypothalamus
Visual field defects
Appetite ↑ or ↓
Wakefulness ↓
Endocrine effects
Cranial nerves 3, 4, 6, 5a
Brainstem
Cranial nerve palsies 3–12, depending on level of tumour
Cerebellar deficit, due to impaired inflow or outflow from the cerebellum
Long tract, motor and sensory, deficits in limbs and trunk
Impaired vital functions i.e. respiration, thermo-regulation and circulation
Cerebellum
Nystagmus
Dysarthria
Limb and gait ataxia

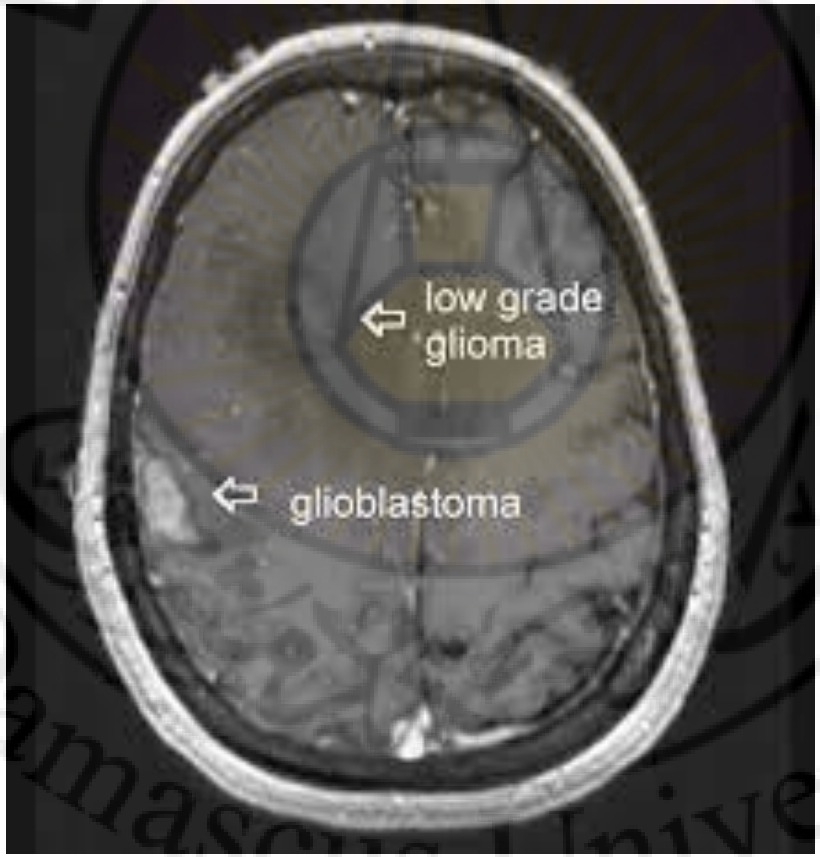
Common brain tumours



Common brain tumours

Gliomas are seen to appear in both the benign and malignant groups of tumours. Astrocytomas are by far the most common glial tumour; tumours derived from oligodendrocytes, ependyma, neurones, primitive neuroectodermal or other tissues are much rarer.

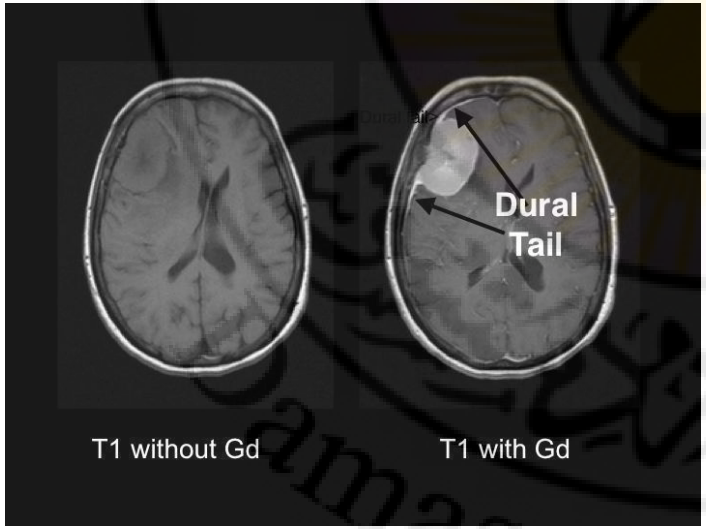
Gliomas are classified histologically from grade 1 (benign) to grade 4 (the highly malignant glioblastoma multiforme).

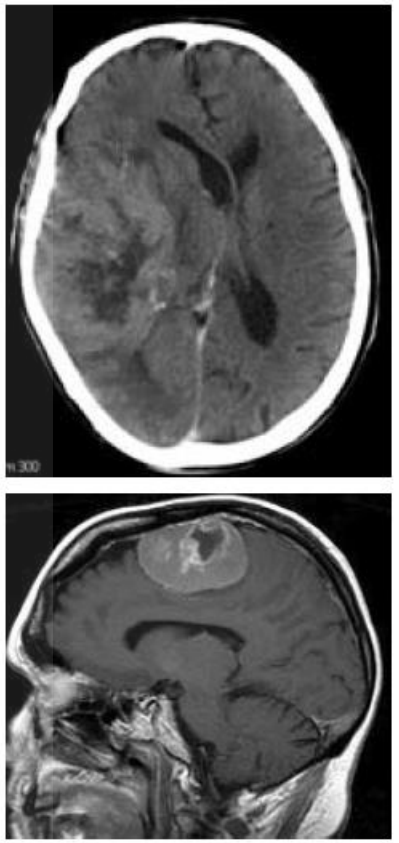


Benign gliomas are, unfortunately, much less common than malignant ones and have a tendency to become more malignant with time.

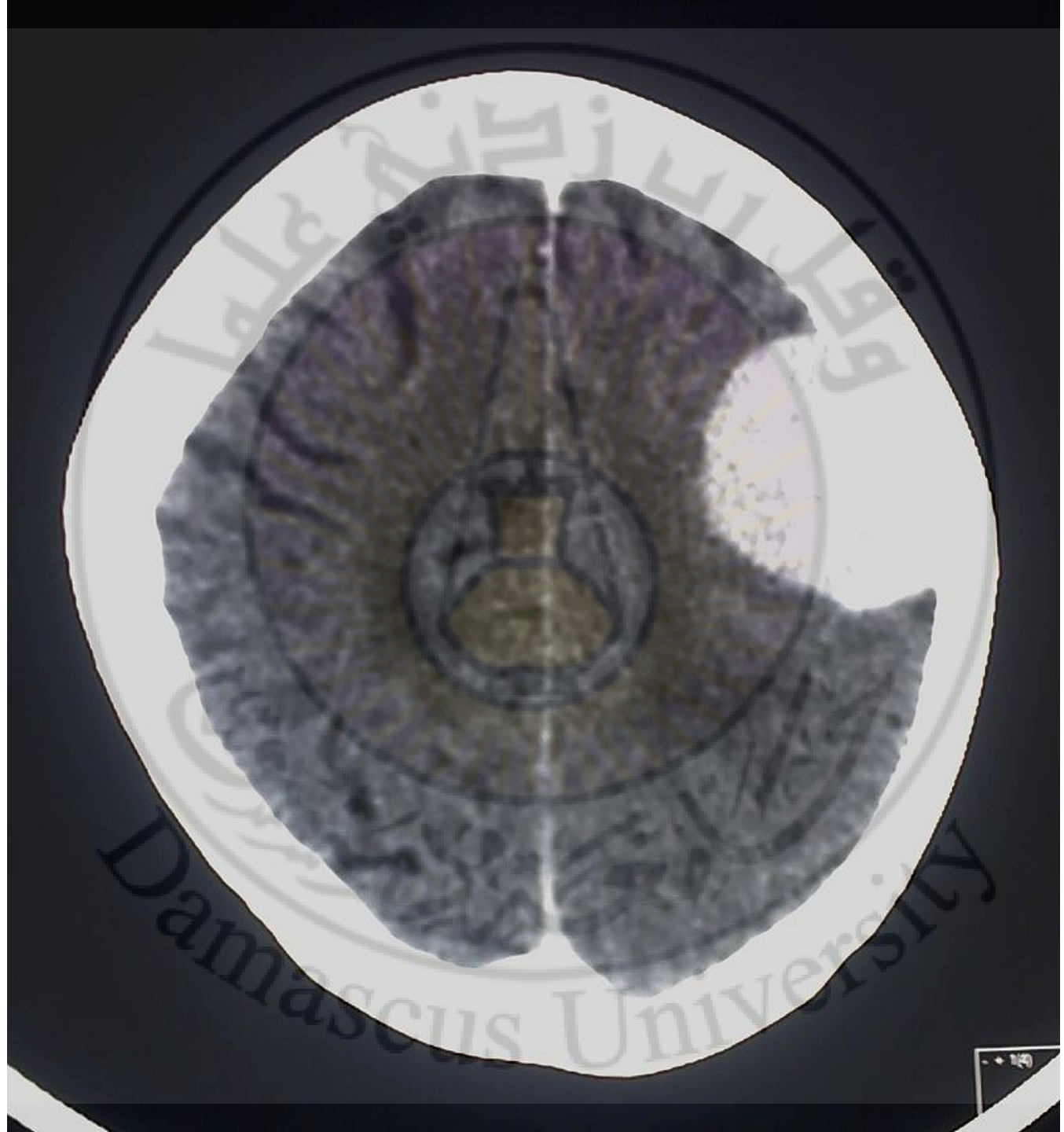
Common brain tumours

Meningiomas are nearly always benign. They may arise from any part of the meninges, over the surface of the brain, from the falx, or from the tentorium. There is a plane of cleavage between tumour and brain tissue which makes total removal a definite possibility, so long as the tumour is reasonably accessible and unattached to dural venous sinuses, e.g. the sagittal sinus.

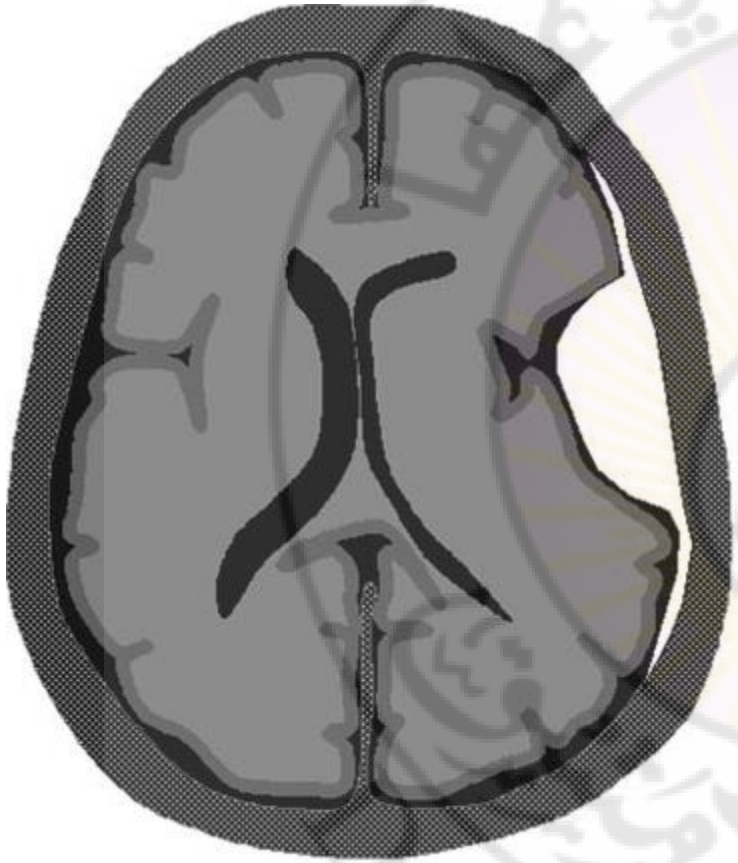




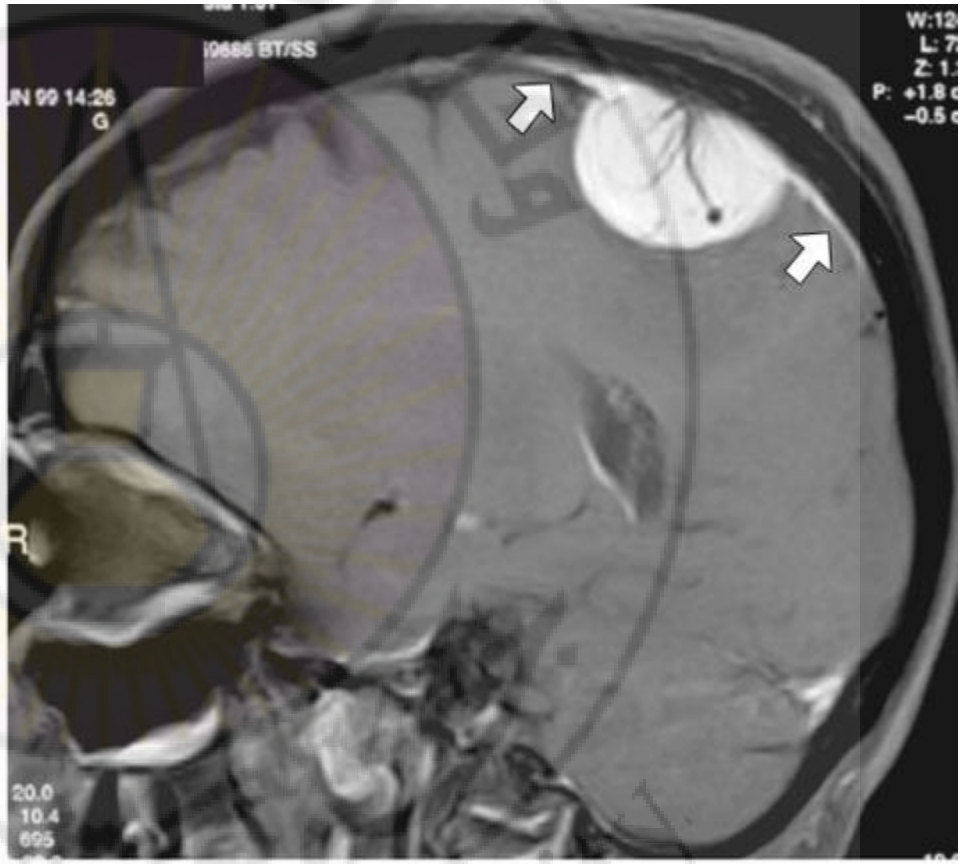
The glioma (top) is poorly differentiated from the surrounding brain, unlike the meningioma (bottom).



Dural tail enhancement with meningioma

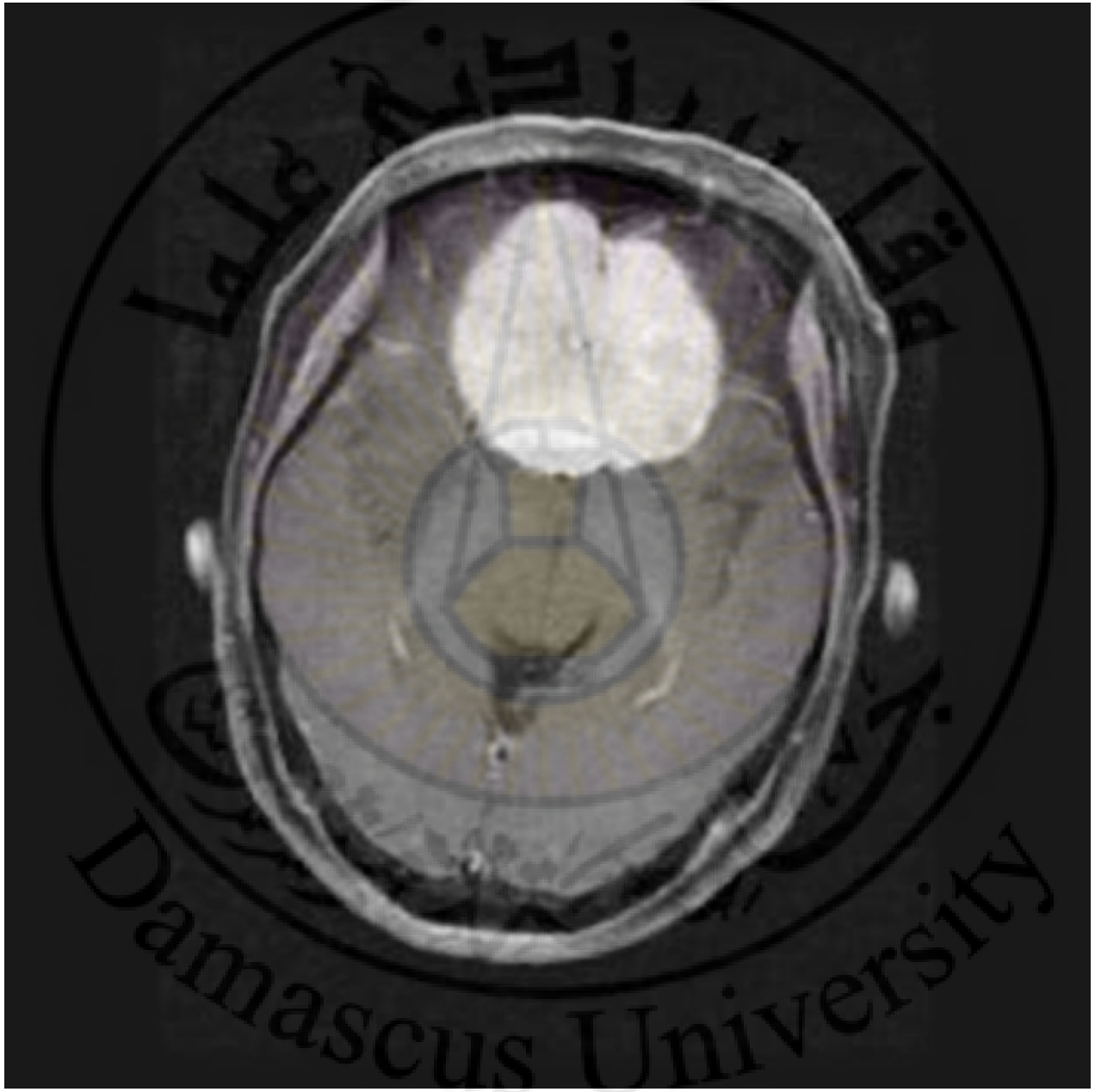


3a.



4.

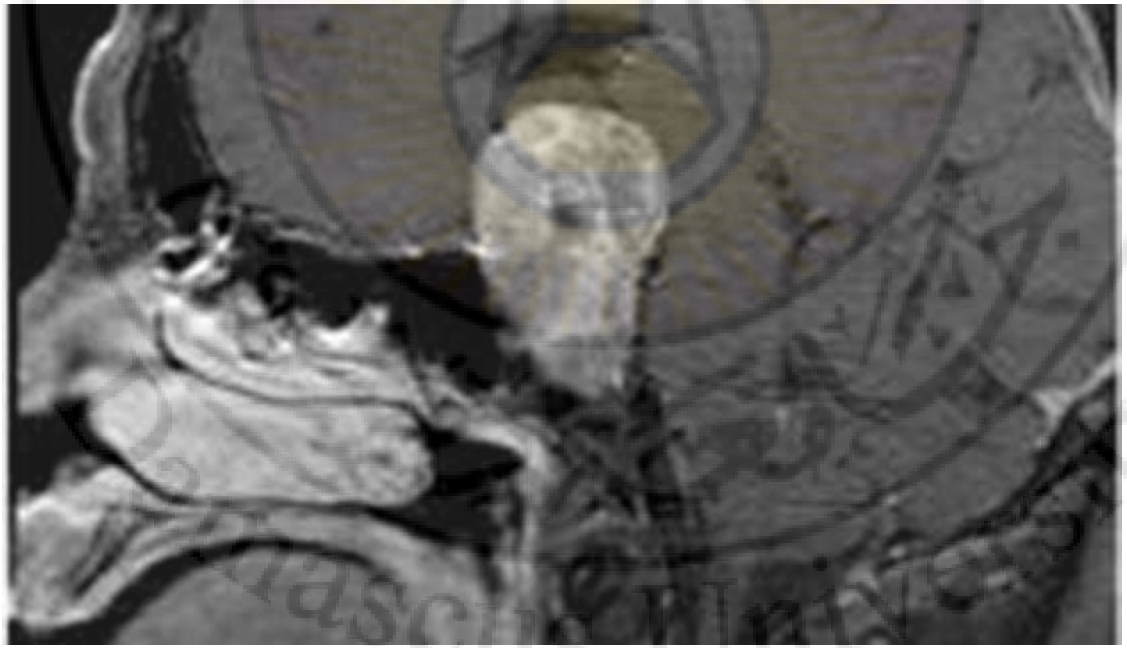
Sagittal gadolinium-enhanced T1-weighted MR image reveals a large extraaxial enhancing mass. The dural tail (arrows) extends several centimeters from the smooth edge of the densely enhancing hemispheric mass. Most of this dural tail enhancement is caused by reactive changes in the dura mater.

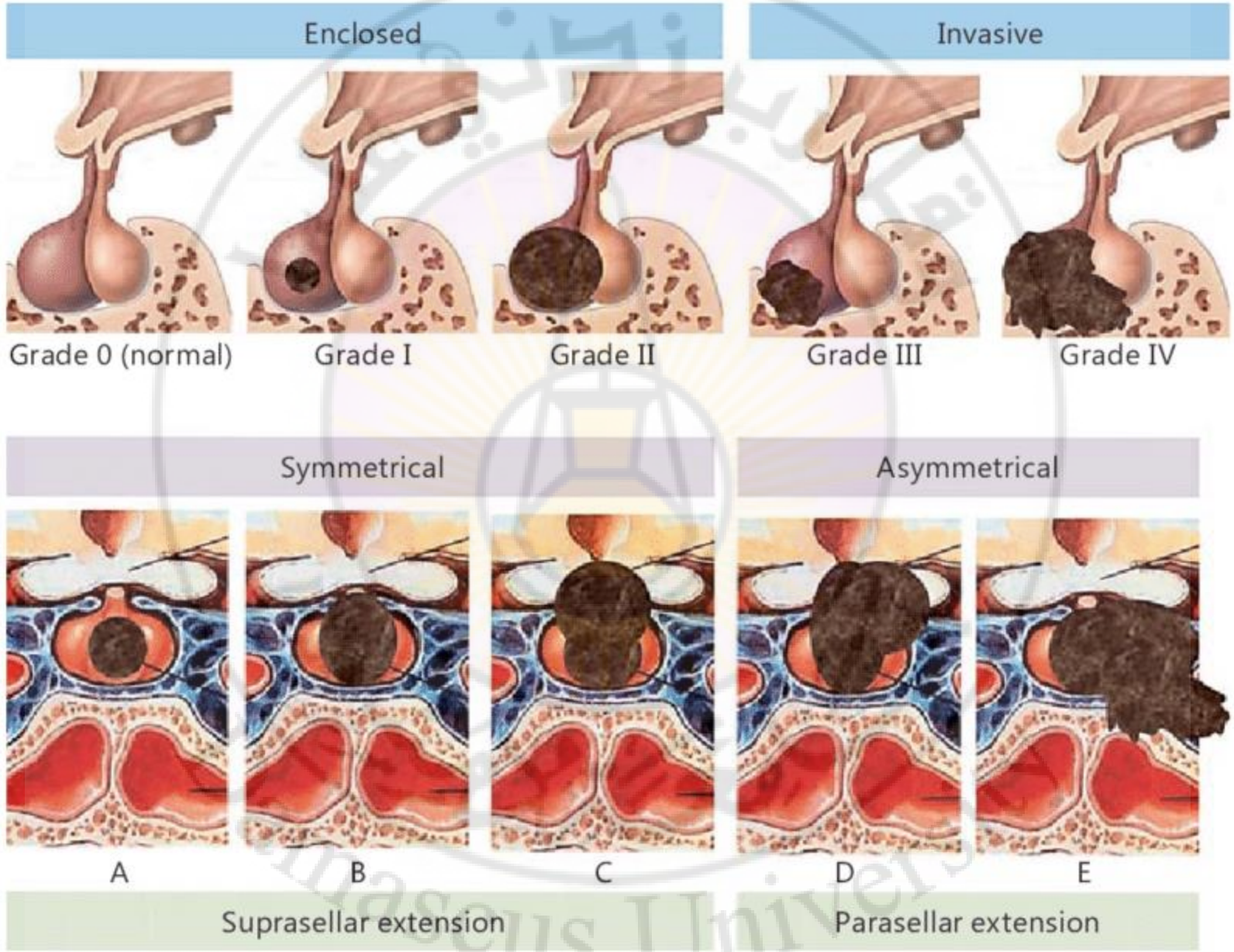


Common brain tumours

Pituitary adenomas **produce two principal sets of symptoms:**

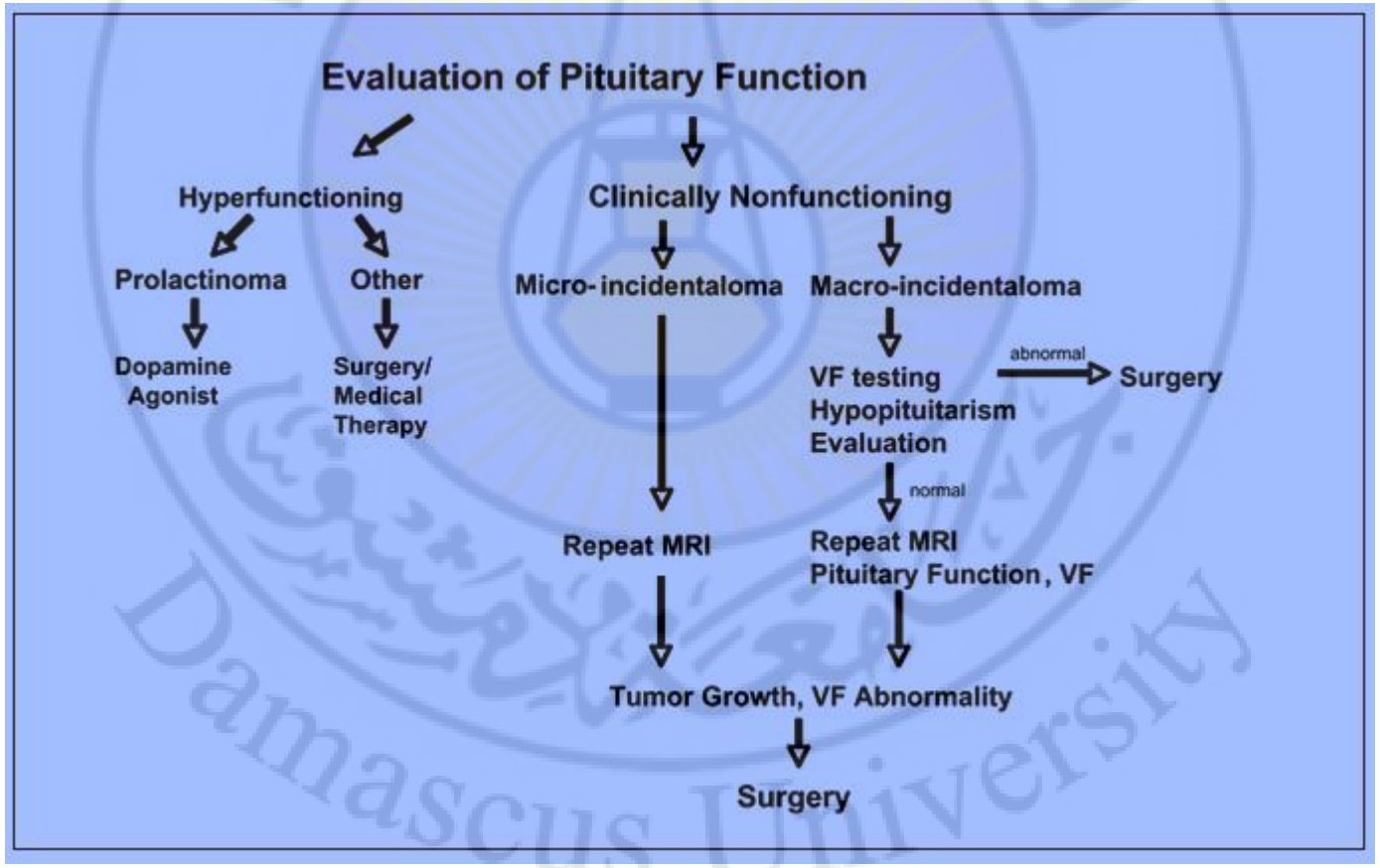
space-occupying effects and endocrine disturbance.




Enclosed
Invasive
Grade 0 (normal)
Grade I
Grade II
Grade III
Grade IV
Symmetrical
Asymmetrical
A
B
C
D
E
Suprasellar extension
Parasellar extension

Bitemporal hemianopia resulting from chiasmal compression

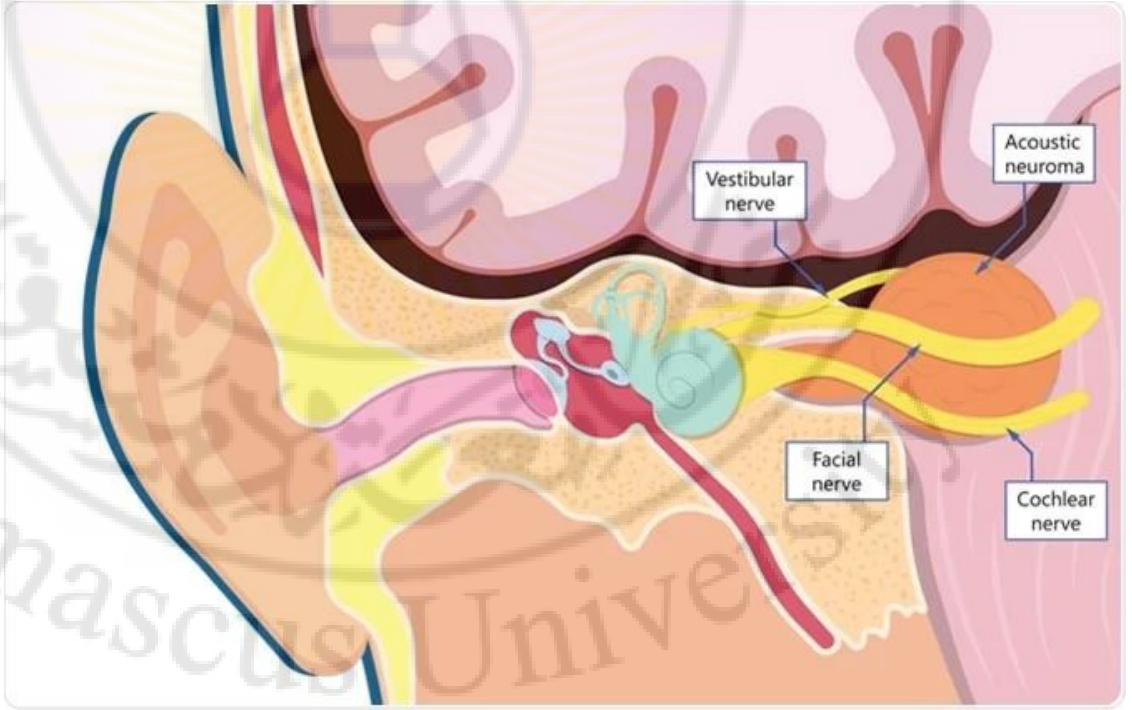
The endocrine disturbances that accompany the development of a pituitary adenoma are *positive* if the tumour cells are secretory (prolactin, growth hormone, etc.), and *negative* if the tumour is preventing normal secretion by the rest of the pituitary gland (varying degrees of panhypopituitarism).



Common brain tumours

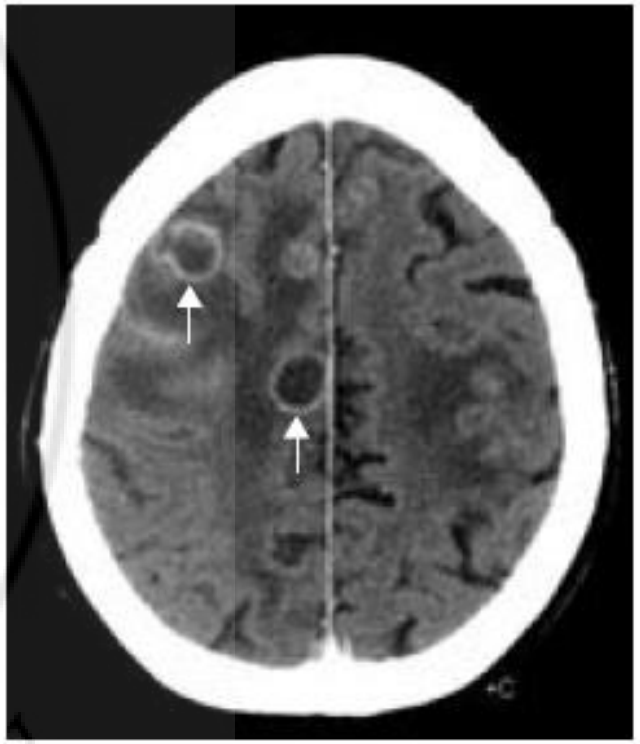
Acoustic neuromas are benign tumours of the Schwann cells along the course of the acoustic nerve, between the cerebellopontine angle and the internal auditory meatus in the petrous temporal bone. First and foremost, they produce progressive unilateral nerve deafness, but by the time of recognition there may well be associated 5th and 7th nerve dysfunction, unilateral cerebellar signs and evidence of raised intracranial pressure.

Early diagnosis is highly desirable since a small tumour can be treated with radiotherapy or surgery with fewer complications than a large one which has caused brainstem displacement and raised intracranial pressure.



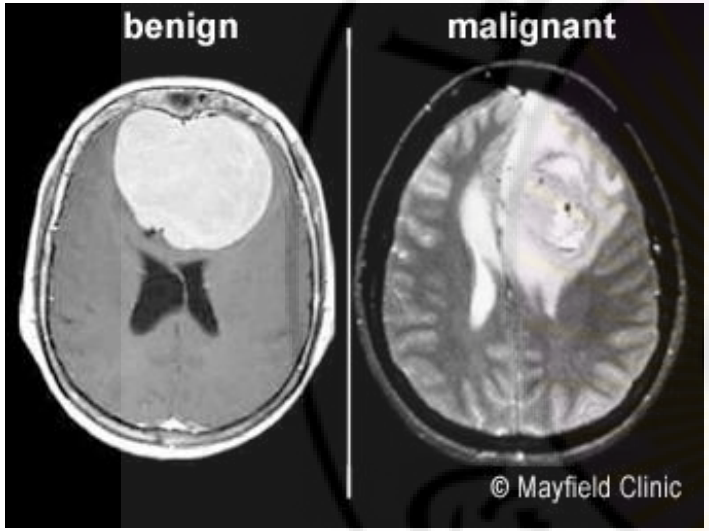
Common brain tumours

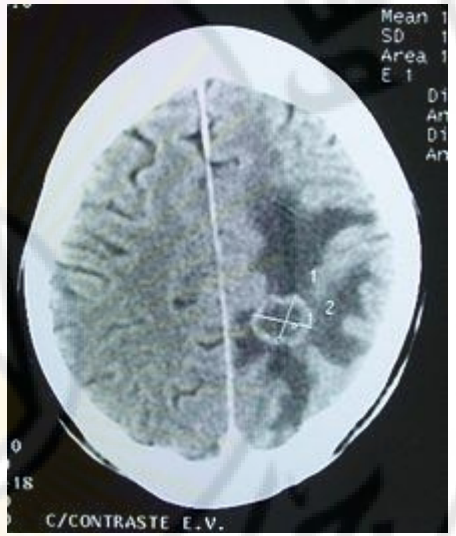
Common malignant tumours in the brain are either *gliomas* or *metastases*, in particular malignant astrocytomas and metastatic carcinoma. Together these constitute well over 60% of all brain tumours. The history is usually short, of raised intracranial pressure, epilepsy or neurological deficit. Not uncommonly, all three groups of symptoms are present by the time of diagnosis. It is not uncommon for a primary carcinoma elsewhere in the body to present with metastatic disease in the brain. If the metastases are multiple, the differentiation from malignant glioma is not difficult, but solitary cerebral metastases are quite common.



Metastases (arrows).

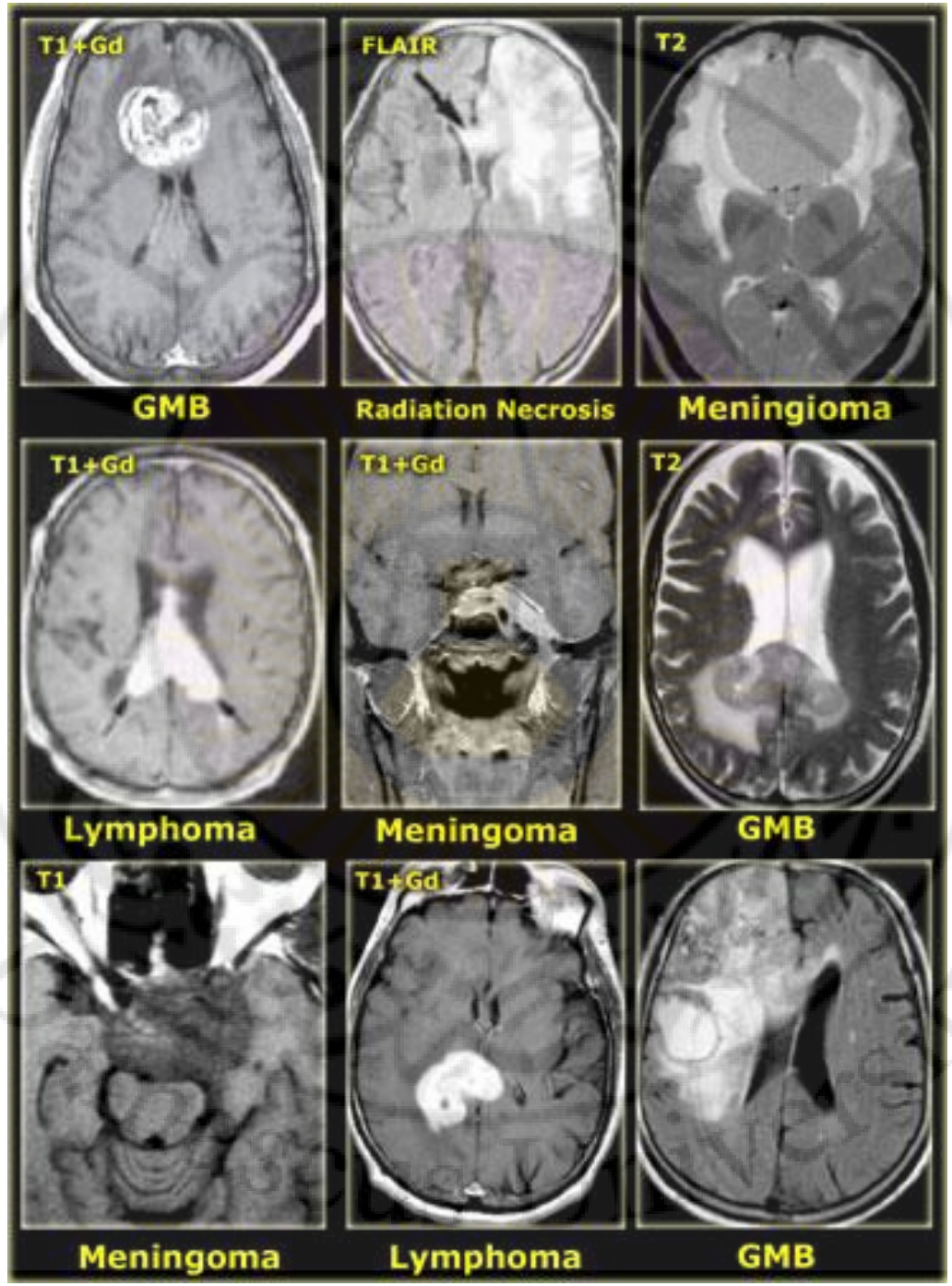
Common brain tumours





Brain imaging

Brain tumours can be detected using CT X-ray scanning or MR scanning. The choice of technique used will often depend upon local facilities. CT is cheaper, more widely available and (when used with contrast enhancement) capable of detecting the majority of tumours. MR scanning is superior in many ways, especially in detecting small tumours and tumours in the base of the skull and the posterior fossa. MR also allows the images to be presented in a range of planes, which helps with surgical planning.


T1+Gd
FLAIR
T2
GMB
Radiation Necrosis
Meningioma
T1+Gd
T1+Gd
T2
Lymphoma
Meningoma
GMB
T1
T1+Gd
Meningoma
Lymphoma
GMB

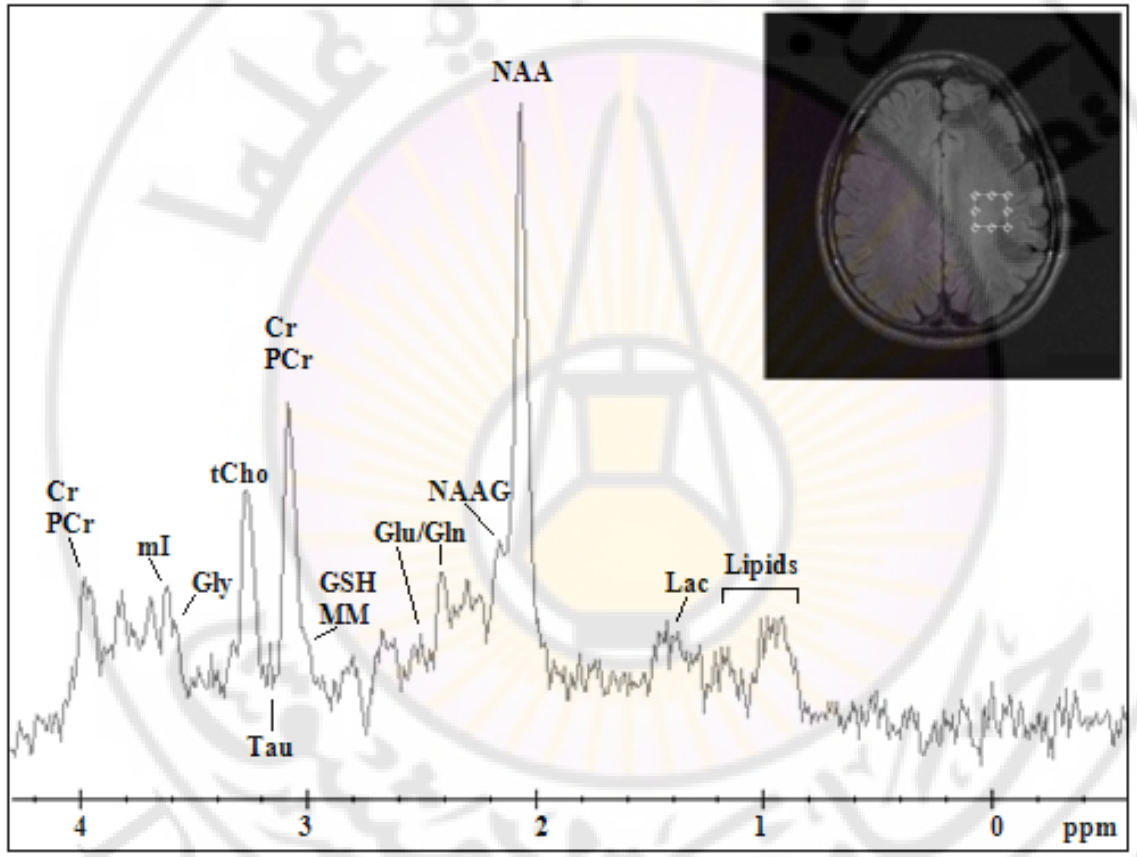
MR Spectroscopy (MRS)

Cr: Energy metabolism

Choline: Metabolism of cell membrane

M-Ino: Glial cell

GABA: Neurotransmiter



NAA: Neuron and axon

Glu: energy metabolism

Tau: Membrane stabilization astrocytes

Lactate: cystic necrotic tissue

Lipids: membrane degeneration marker, necrosis marker

- So in MR spectroscopy (MRS) :-
  - **NAA** is considered as a **good** metabolite (as it represents neuronal health)
  - **Choline** is considered as a **bad** metabolite (as it is seen in tumors) and
  - **Lipid lactate** doublet as an **ugly** metabolite (as it is seen in necrotic tumors).

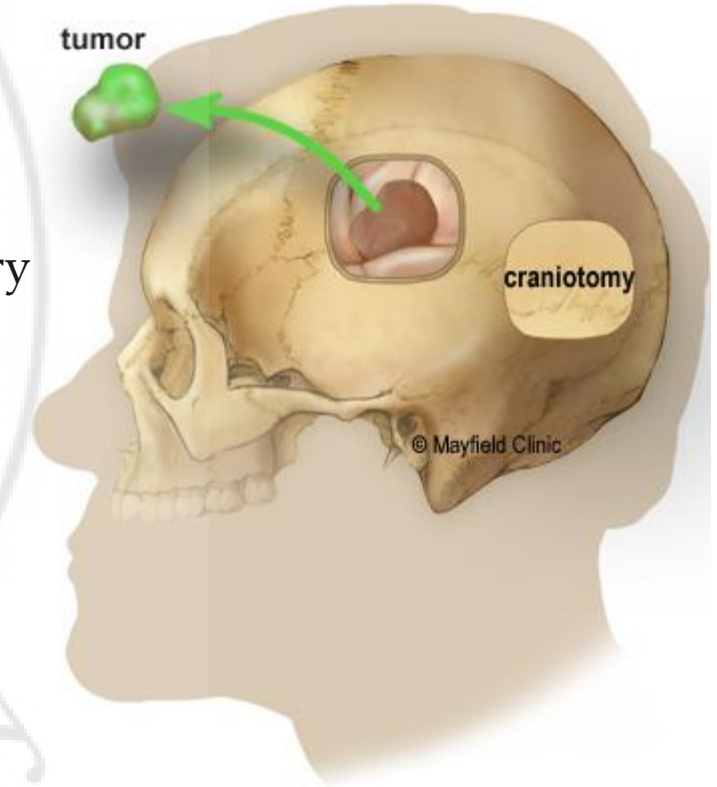
Management of brain tumours

- Admission to hospital
- Scanning
- No lumbar puncture
- Dexamethasone
- Surgery
- Radiotherapy
- Anticonvulsants

Surgical management

Complete removal

Meningiomas, pituitary tumours not susceptible to medical treatment, acoustic neuromas and some solitary metastases in accessible regions of the brain can all be removed completely. Sometimes, the neurosurgical operation required is long and difficult if the benign tumour is relatively inaccessible.



Surgical management

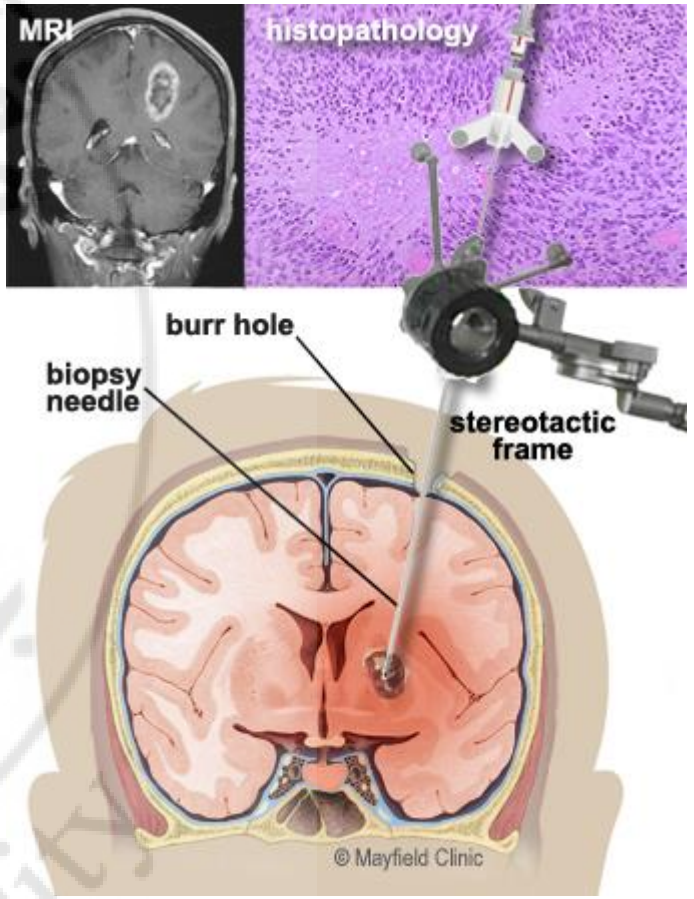
Partial removal

Gliomas in the frontal, occipital and temporal poles may be removed by fairly radical debulking operations. Sometimes, benign tumours cannot be removed in their entirety because of tumour position or patient frailty.

Surgical management

Biopsy

If at all possible, the histological nature of any mass lesion in the brain should be established. What looks like a glioma or metastasis from the clinical and radiological points of view occasionally turns out to be an abscess, a benign tumour or a granuloma.
If the mass lesion is not in a part of the brain where partial removal can be attempted, biopsy by means of a needle through a burrhole usually establishes the histological diagnosis. The accuracy and safety of this procedure may be increased by use of stereotactic surgical techniques. Histological confirmation may not be mandatory where there is strong collateral evidence of metastatic disease.

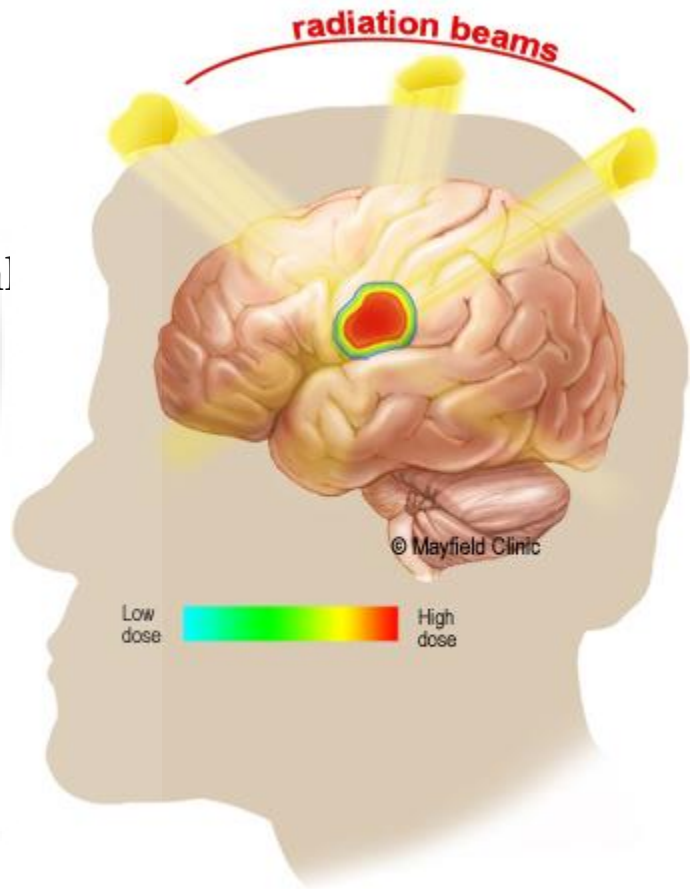


Shunting and endoscopic surgery

Midline tumours causing ventricular dilatation are routinely treated by the insertion of a shunt into the dilated ventricular system. The shunt tubing is tunnelled under the skin to drain into the peritoneal cavity. This returns intracranial pressure to normal, and may completely relieve the patient's symptoms.
Sometimes it is possible and desirable to remove the tumour or treat the hydrocephalus using intracranial endoscopic procedures instead.

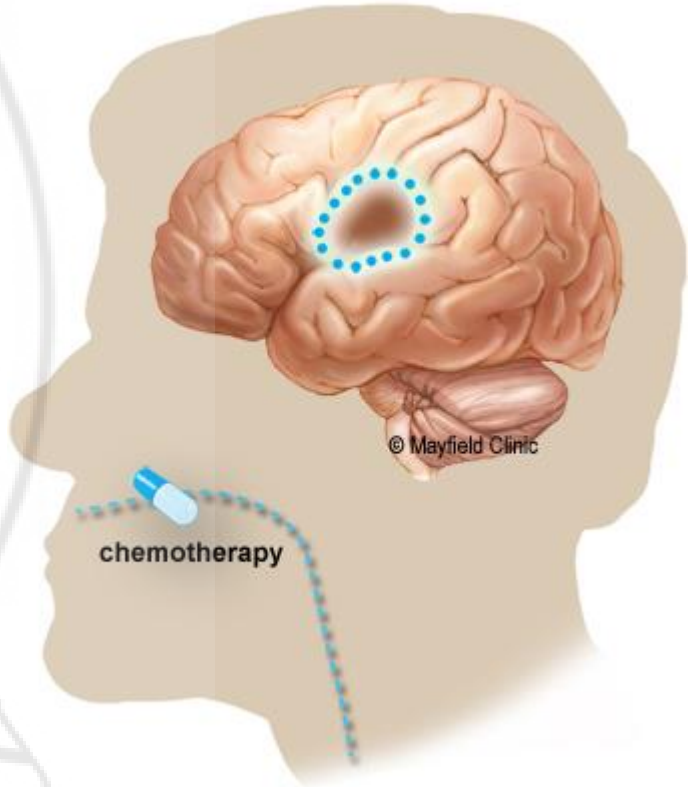
Radiotherapy

Middle-grade gliomas, metastases and incompletely removed pituitary adenomas are the common intracranial tumours which are radiosensitive. The posterior fossa malignant tumours of childhood and lymphoma are also sensitive to radiotherapy.
Radiotherapy commonly follows partial removal or biopsy of such lesions, and continues over a few weeks whilst the preoperative



Chemotherapy

Chemotherapy can be useful as primary treatment for lymphoma and as adjunctive therapy for oligodendroglioma and some high-grade astrocytomas.



Anticonvulsants

Control of epilepsy may be an important part of the management of a patient with a supratentorial brain tumour.

Dexamethasone

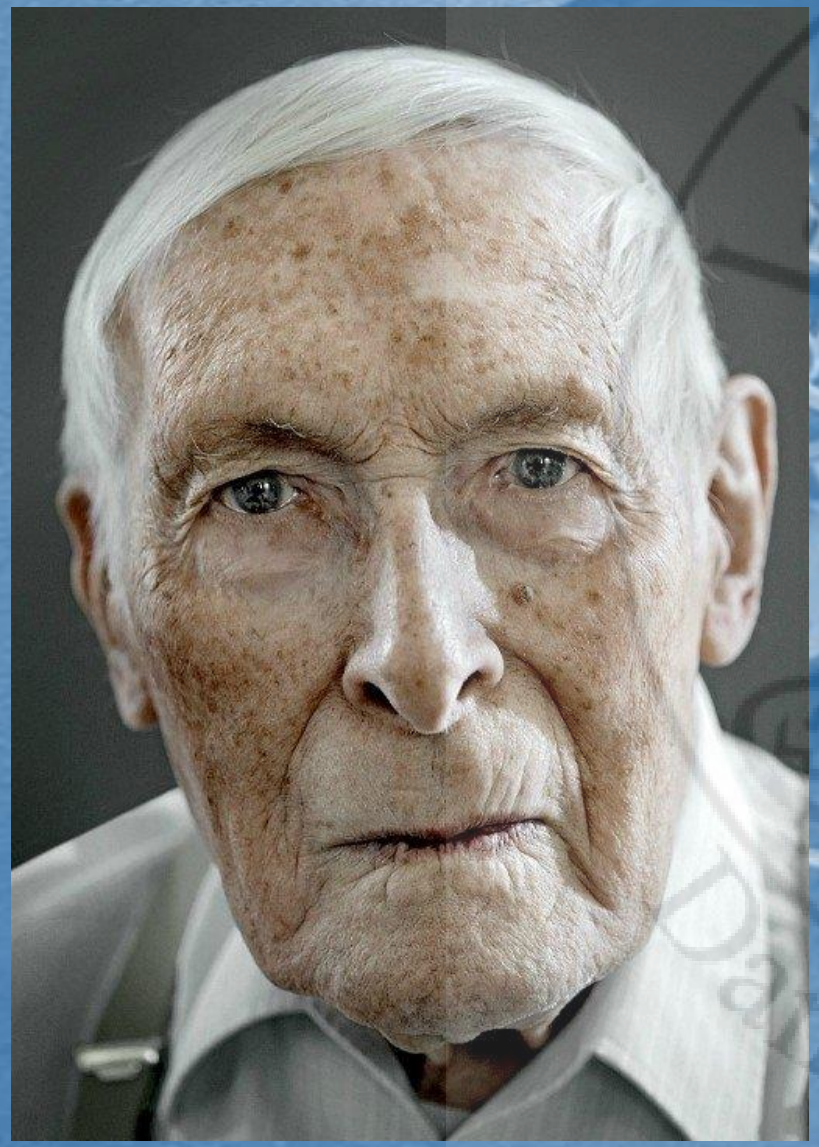
Taken in large and constant dosage, dexamethasone may be the most humane treatment of patients with highly malignant gliomas or metastatic disease. Used in this way, dexamethasone often allows significant symptomatic relief so that the patient can return home and enjoy a short period of dignified existence before the tumour once more shows its presence. At this point, dexamethasone can be withdrawn and opiates used as required.

Prognosis

The fact that the majority of brain tumours are either malignant gliomas or metastases, which obviously carry a very poor prognosis, hangs like a cloud over the outlook for patients with the common brain tumours.
The table below summarizes the outlook for patients with the common brain tumours. It can be seen that such pessimism is justified for malignant brain tumours, but not for the less common benign neoplasms.

Tumour	Treatment	Outcome
Meningioma	Surgical removal if possible and/or radiotherapy if not	Residual disability common Recurrence rate (1% per year)
Glioma		
Lower grades	Watch and wait *or* biopsy and radiotherapy *or* partial removal ± radiotherapy ± chemotherapy	Prolonged survival, usually with residual disability, but recurrence is very common and often higher grade
High grade	Partial removal and radiotherapy ± chemotherapy or palliative care	Few patients survive 1 year
Lymphoma	Biopsy and chemotherapy	Improving: median survival about 2 years
Pituitary adenoma	Medical therapy for prolactinoma *or* surgical removal ± radiotherapy	Excellent
Acoustic neuroma	Watch and wait *or* radiotherapy *or* surgical removal	Deafness ± facial weakness are common; survival is excellent


THE END
THANK YOU FOR YOUR ATTENTION

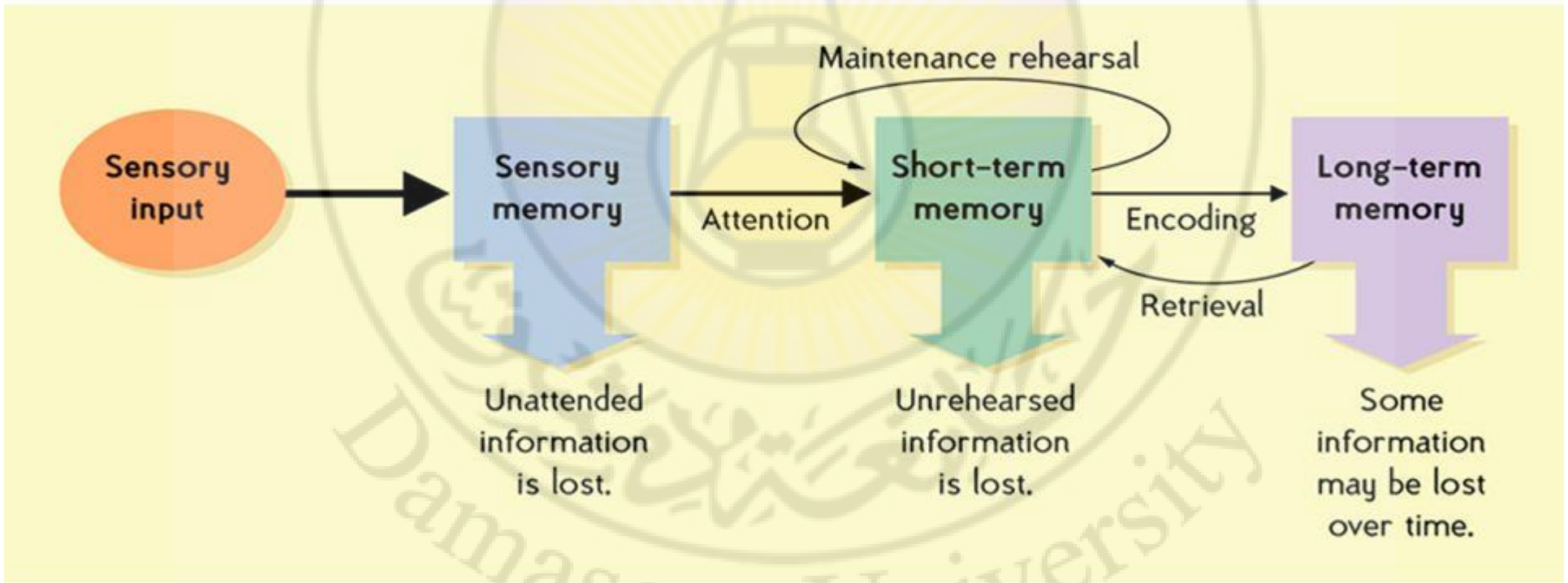


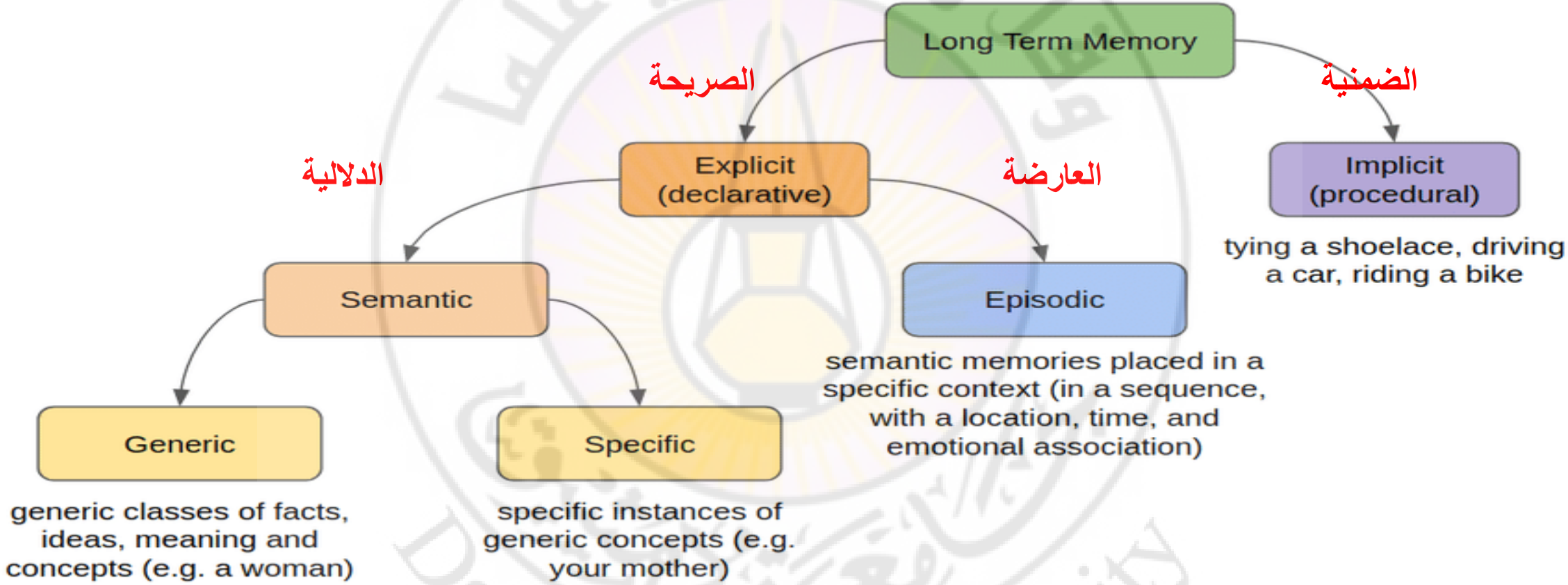
Dementia

Professor Mohamad Shehadeh Agha
MD MRCP (London) FRCP (Edin)

The Basic Stages of Memory

The Modal Memory Model





Episodic memory refers to information that is encoded along a spatial and temporal plane

Semantic memory refers to memory that is encoded with specific meaning

1. **Frontal lobe**
The frontal lobes store semantic and episodic memories.

2. **Motor cortex**
The mortor cortex is involved in storing procedural memories.

7. **Prefrontal cortex**
The prefrontal cortex is involved in the storage of short-term memories.

3. **Cerebellum**
The cerebellum plays an important role in the storage of procedural memories.

6. **Temporal lobe**
The temporal lobe is involved in the formation and storage of long-term semantic and episodic memories and contributes to the processing of new material in short-term memory.

5. **Amygdala**
The amygdala is vital to the *formation* of new emotional memories.

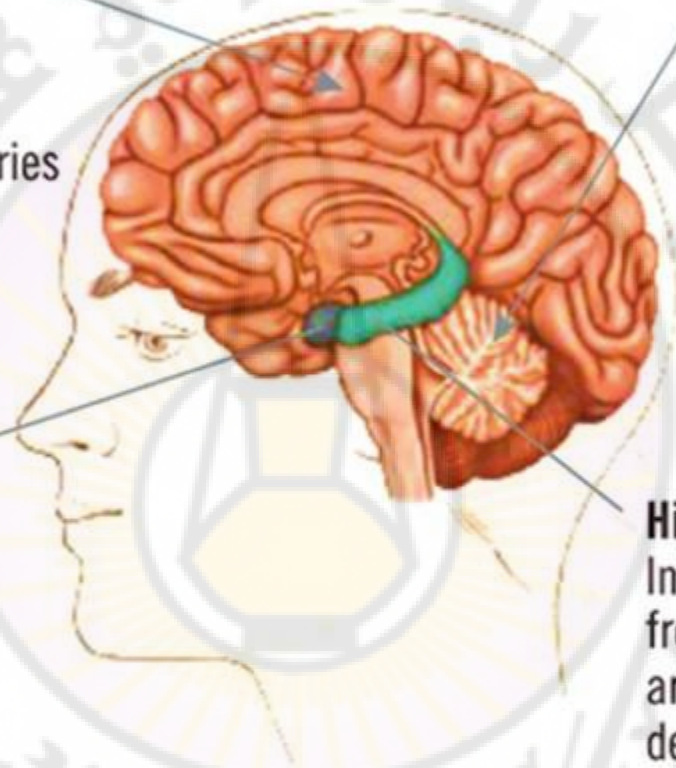
4. **Hippocampus**
The hippocampus plays a pivotal role in the *formation* of new long-term semantic and episodic memories.

STORAGE = Cerebral cortex – explicit memories, stored depending on type of memory

Cerebral cortex
Involved in the formation and storage of implicit and explicit memories

Cerebellum
Stores procedural memories of learnt motor skills that require muscle coordination

STORAGE/ ENCODING = Cerebellum
Both procedural and classically conditioned reflex responses



ENCODING = Amygdala – triggers encoding from STM to LTM of emotionally arousing experiences

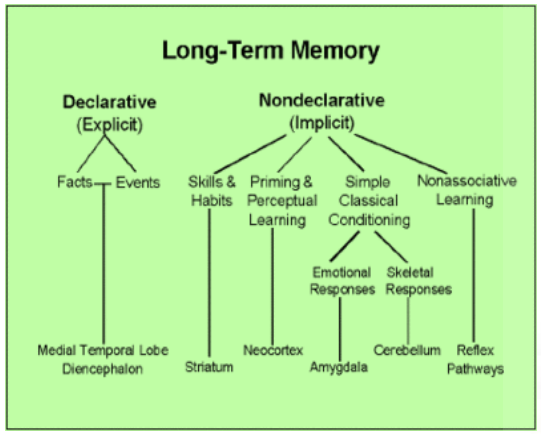
Amygdala
Adds the emotional content to declarative memories

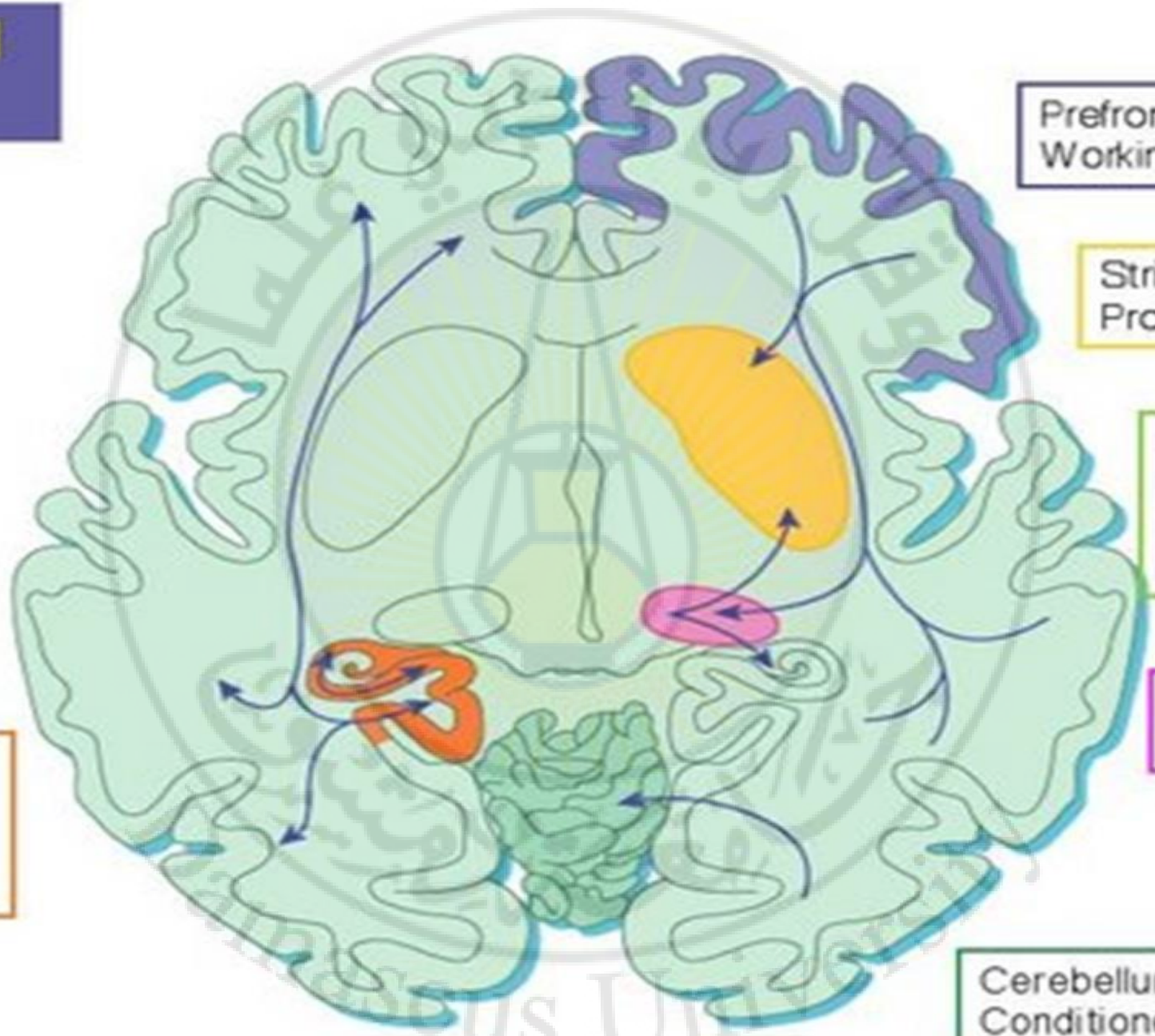
Hippocampus
Integrates information from a number of brain areas to form a single declarative memory that it transfers to long-term memory

ENCODING = Hippocampus – facilitates transfer from STM to LTM

FIGURE 5.10 The cerebral cortex, hippocampus, amygdala and cerebellum are all involved in the formation and storage of long-term memories.

Memory and the Brain





Prefrontal cortex:
Working memory

Striatum:
Procedural memory

Cerebral cortex:
Perceptual memory,
semantic memory,
priming

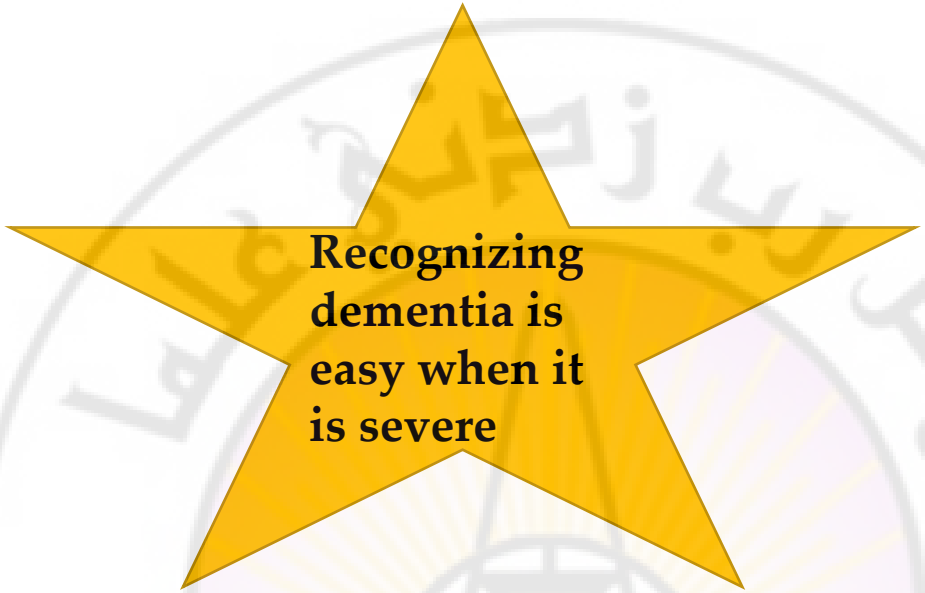
Amygdala:
Emotional memory

Hippocampus:
Dedarative memory
--Episodic memory
--Semantic memory

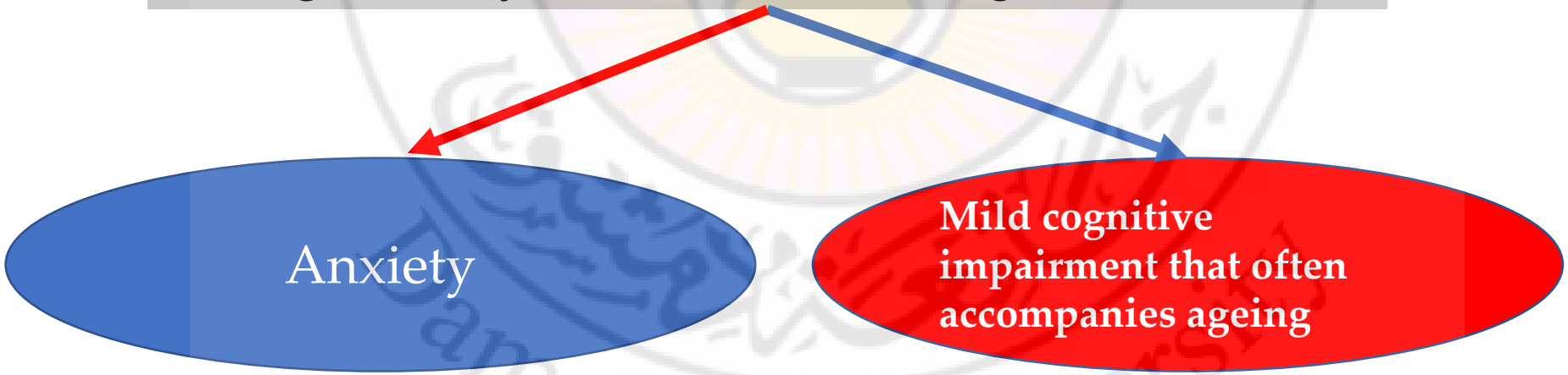
Cerebellum:
Conditioned timing

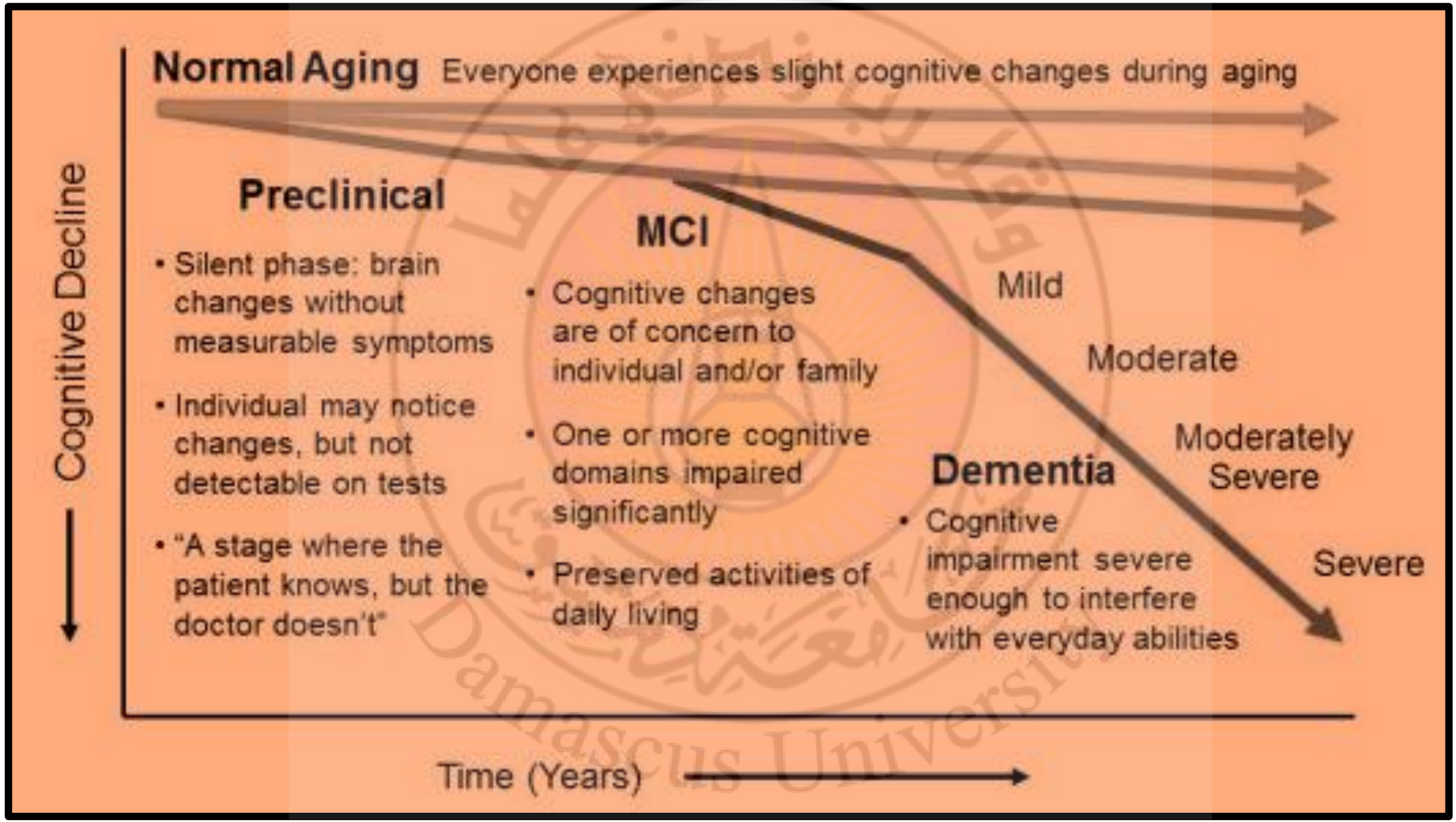
Dementia

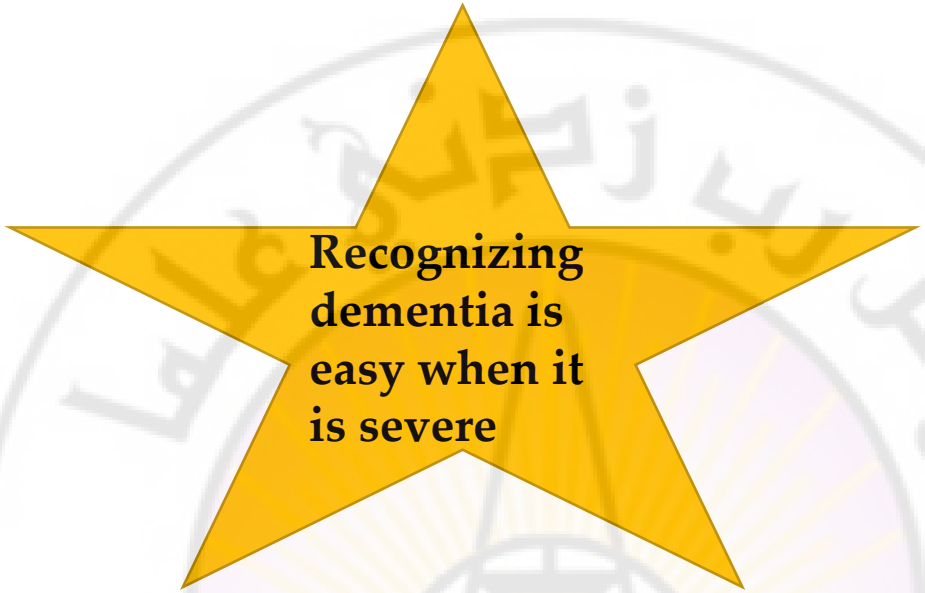
- Progressive
- Involvement of more than one area of intellectual function (such as memory, language, judgement or visuospatial ability)
- Sufficiently severe to disrupt daily life



Distinguish early dementia from the forgetfulness due to




Normal Aging Everyone experiences slight cognitive changes during aging
Cognitive Decline
Preclinical
• Silent phase: brain changes without measurable symptoms
• Individual may notice changes, but not detectable on tests
• "A stage where the patient knows, but the doctor doesn't"
MCI
• Cognitive changes are of concern to individual and/or family
• One or more cognitive domains impaired significantly
• Preserved activities of daily living
Mild
Moderate
Moderately Severe
Severe
Dementia
• Cognitive impairment severe enough to interfere with everyday abilities
Time (Years)



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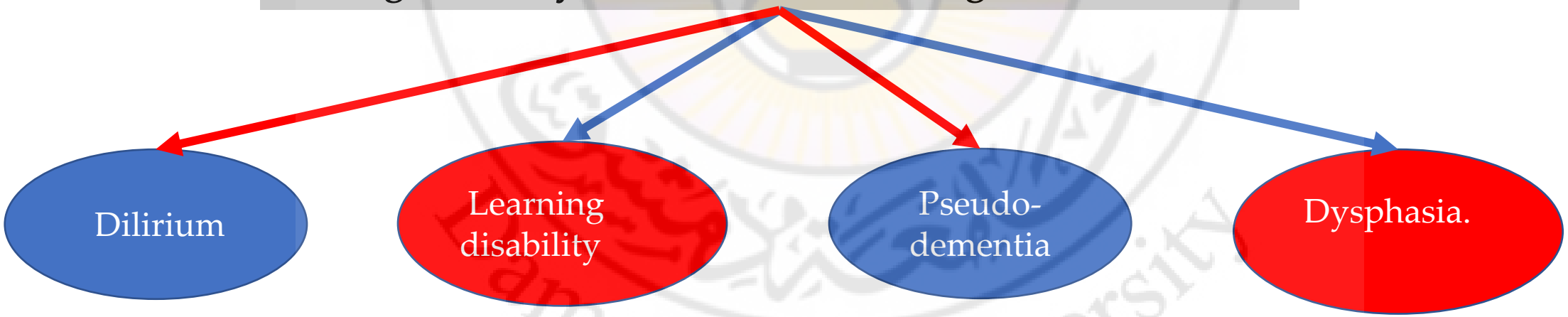


Delirium
(acute confusional state)

Delirium is a state of confusion in which patients are not fully in touch with their environment. They are drowsy, perplexedand uncooperative.

Subtypes of Delirium

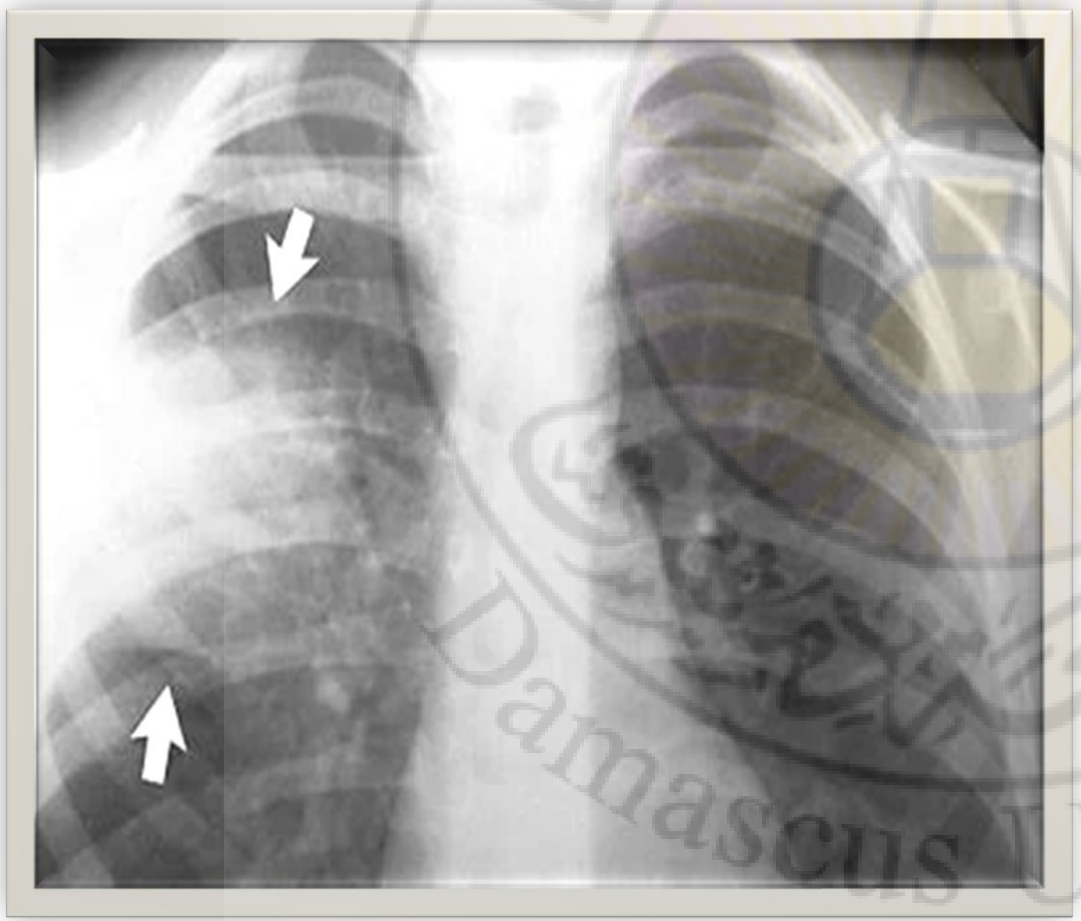
- Subtypes: three subtypes-
  - Hyperactive delirium
  - Hypoactive delirium
  - Mixed type.

- Hyperactive delirium is characterised by agitation, restlessness and attempts to remove invasive tools.(Drug Intoxication)
- Hypoactive delirium is characterised by withdrawal, flat affect, apathy, lethargy and decreased responsiveness.
- Mixed delirium occurs when the patient's symptoms fluctuate between the two conditions .

Majors causes of Delirium

- Metabolic
- Toxic
- Infectious
- Neurologic
- Perioperative

Two important tests



Treatment

- Haloperidol – max dose upto 5 mg
- Atypical antipsychotics— risperidone, olanzapine, quetiapine, and aripiprazole
- Valproate ,ondansateron, Melatonin

- Recent evidence indicates that low dose melatonin and Ramelteon, a melatonin receptor agonist, are effective at lowering the risk of delirium .
- **NEWER DRUG**: Dexmedetomidine, (alpha-2 agonist)

Learning disability

Learning disability is the currently accepted term for a condition that has in the past been referred to as mental retardation, mental handicap or educational subnormality..

The difference between dementia and learning disability is that patients with dementia have had normal intelligence in their adult life and then start to lose it, whereas patients with learning disability have suffered some insult to their brains early in life which has prevented the development of normal intelligence.

While dementia is progressive, learning disability is static unless a further insult to the brain occurs. The person with learning disability learns and develops, slowly and to a limited extent

Learning disability

Early disruption of brain function results in any of:

1. Impaired thinking, reasoning, memory, language, etc.
2. Behaviour problems because of difficulty in learning social customs, controlling emotions or appreciating the emotional needs of others.
3. Abnormal movement of the body, because of damage to the parts of the brain involved in movement (motor cortex, basal ganglia, cerebellum, thalamus, sensory cortex) giving rise to:
   - delayed milestones for sitting, crawling, walking;
   - spastic forms of cerebral palsy including congenital hemiplegia and spastic diplegia (or tetraplegia);
   - dystonic (‘athetoid’) form of cerebral palsy (where the intellect is often normal);
   - clumsy, poorly coordinated movement;
   - repetitive or ritualistic stereotyped movements.
4. Epilepsy, which may be severe and resistant to treatment.

Genetic abnormality
e.g. Down's syndrome
Fragile X syndrome

Intra-uterine event
e.g. Infection
Stroke
Drug exposure

Birth anoxia

Insult early in life
e.g. Meningitis
Head injury
Non-accidental injury

Young

Brain

Low IQ

Movement disorder

Epilepsy

Behaviour problems

Learning disability

Pseudodementia

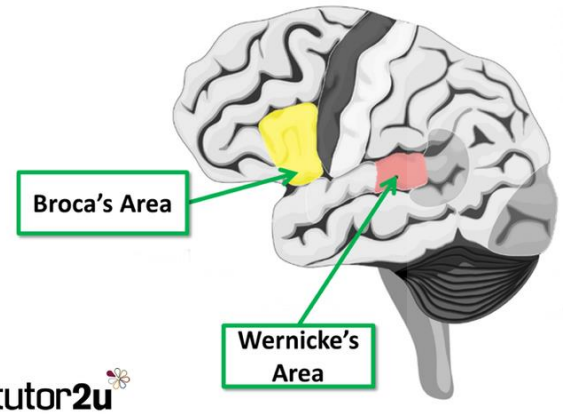
The history is often short and abrupt onset

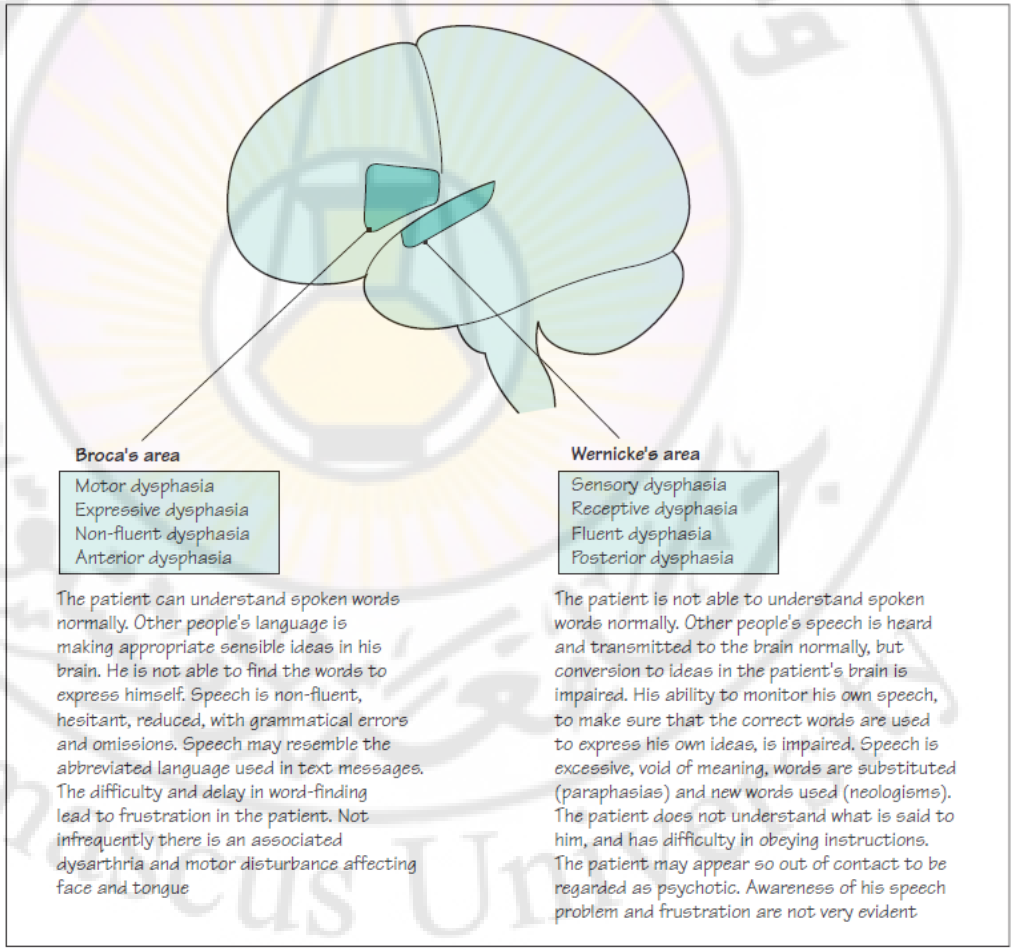
Their overall functional performance, at work or in the house, may become grossly impaired because of mental slowness, indecisiveness, lack of enthusiasm and impaired energy

'. . . I can't remember . . I think you'd better ask my wife . .'

They will often answer that they don't know the answer to a question, and their attention and concentration are often intact

Dysphasia





Broca's area

Motor dysphasia
Expressive dysphasia
Non-fluent dysphasia
Anterior dysphasia

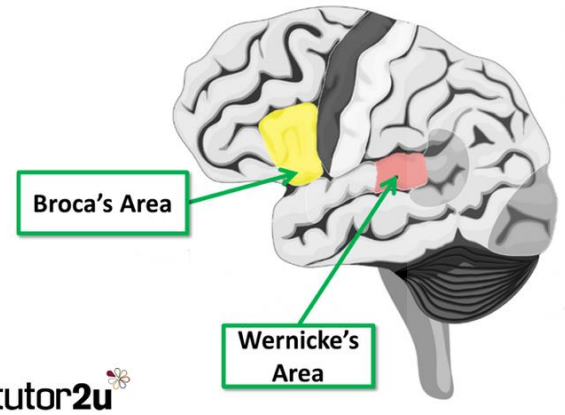
The patient can understand spoken words normally. Other people's language is making appropriate sensible ideas in his brain. He is not able to find the words to express himself. Speech is non-fluent, hesitant, reduced, with grammatical errors and omissions. Speech may resemble the abbreviated language used in text messages. The difficulty and delay in word-finding lead to frustration in the patient. Not infrequently there is an associated dysarthria and motor disturbance affecting face and tongue

Wernicke's area

Sensory dysphasia
Receptive dysphasia
Fluent dysphasia
Posterior dysphasia

The patient is not able to understand spoken words normally. Other people's speech is heard and transmitted to the brain normally, but conversion to ideas in the patient's brain is impaired. His ability to monitor his own speech, to make sure that the correct words are used to express his own ideas, is impaired. Speech is excessive, void of meaning, words are substituted (paraphasias) and new words used (neologisms). The patient does not understand what is said to him, and has difficulty in obeying instructions. The patient may appear so out of contact to be regarded as psychotic. Awareness of his speech problem and frustration are not very evident

Dysphasia



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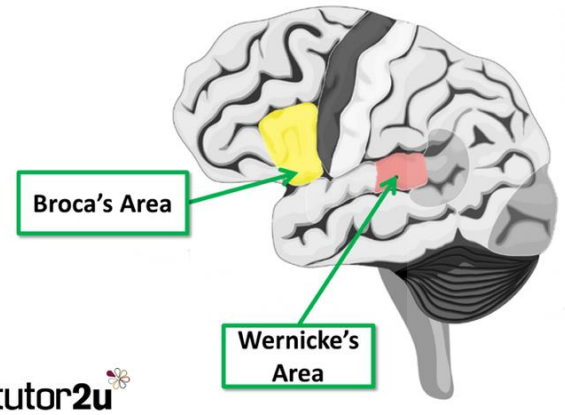
Dysphasia



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Dysphasia

Patients with dysphasia have a language problem. This is not dissimilar to being in a foreign country and finding oneself unable to understand (receptive dysphasia), or make oneself understood (expressive dysphasia).

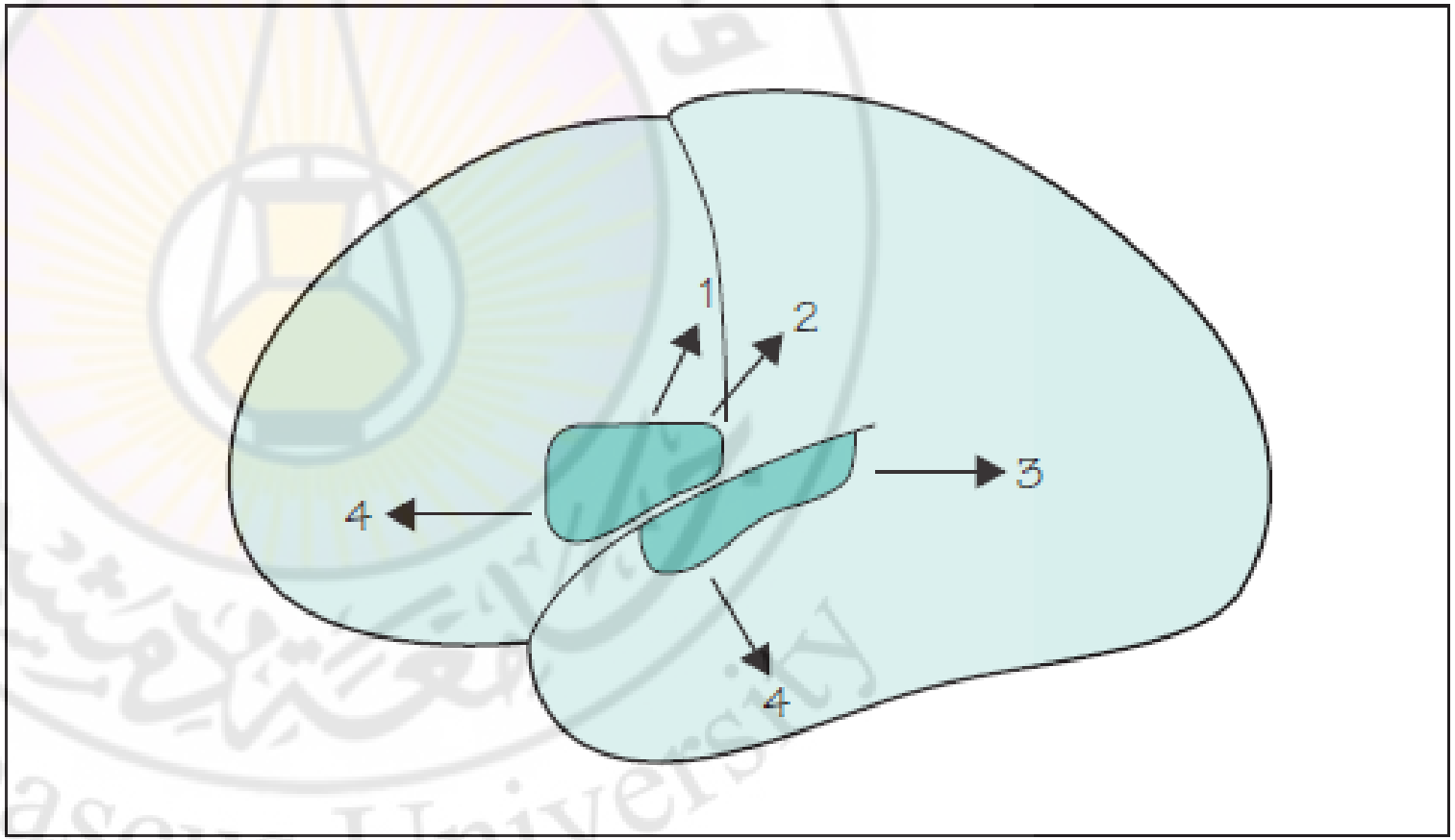
Dysphasia

1 Weakness of the right face, hand and arm

2 Sensory impairment in the right face, hand and arm

3 Difficulties with:
written words . . . dyslexia and dysgraphia
numbers . . . dyscalculia
visual field . . . right homonymous hemianopia

4 Impairment of memory, alteration of behaviour



The common associated neurological abnormalities in dysphasic patients

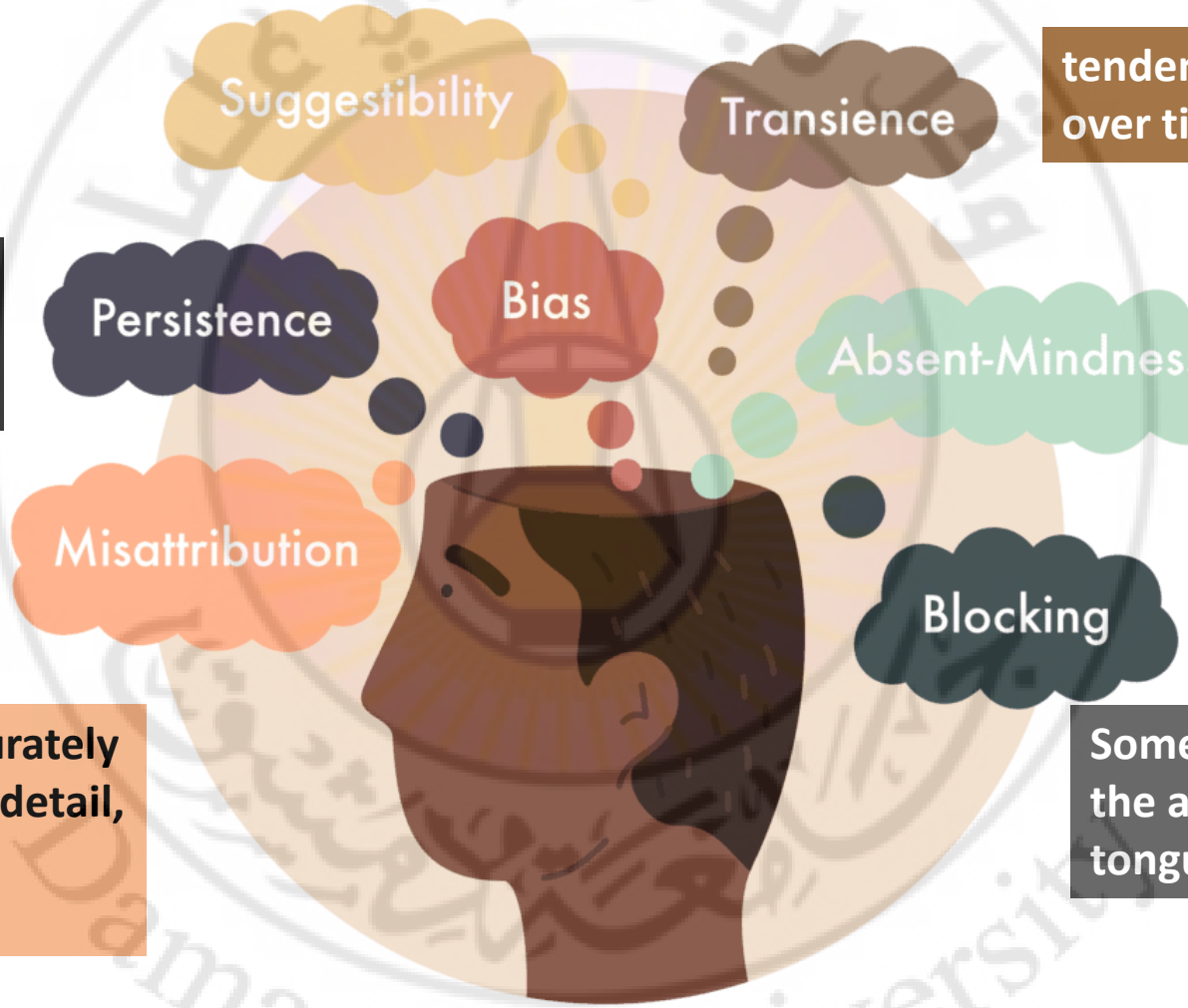
النسيان

السبع أنواع الاعتيادية لاضطراب الذاكرة
Sins of Omission خطايا التقصير

1. **Transience:** سرعة الزوال tendency to forget facts or events over time
2. **Absentmindedness:** شرود الذهن occurs when you don't pay close enough attention
3. **Blocking:** الحجب Someone asks you a question and the answer is right on the tip of your tongue

4. **Misattribution:** سوء النسب you remember something accurately in part, but misattribute some detail, like the time, place, or person involved
5. **Suggestibility:** الايحاء the fact becomes incorporated into your memory of the incident, even though you did not experience these details
6. **Bias:** الانحياز when you retrieve a memory, your mood and other biases at that moment can influence what information you actually recall
7. **Persistence:** الاصرار people are tormented by memories they wish they could forget, but can't

the fact becomes incorporated into your memory of the incident, even though you did not experience these details



tendency to forget facts or events over time

people are tormented by memories they wish they could forget, but can't

occurs when you don't pay close enough attention

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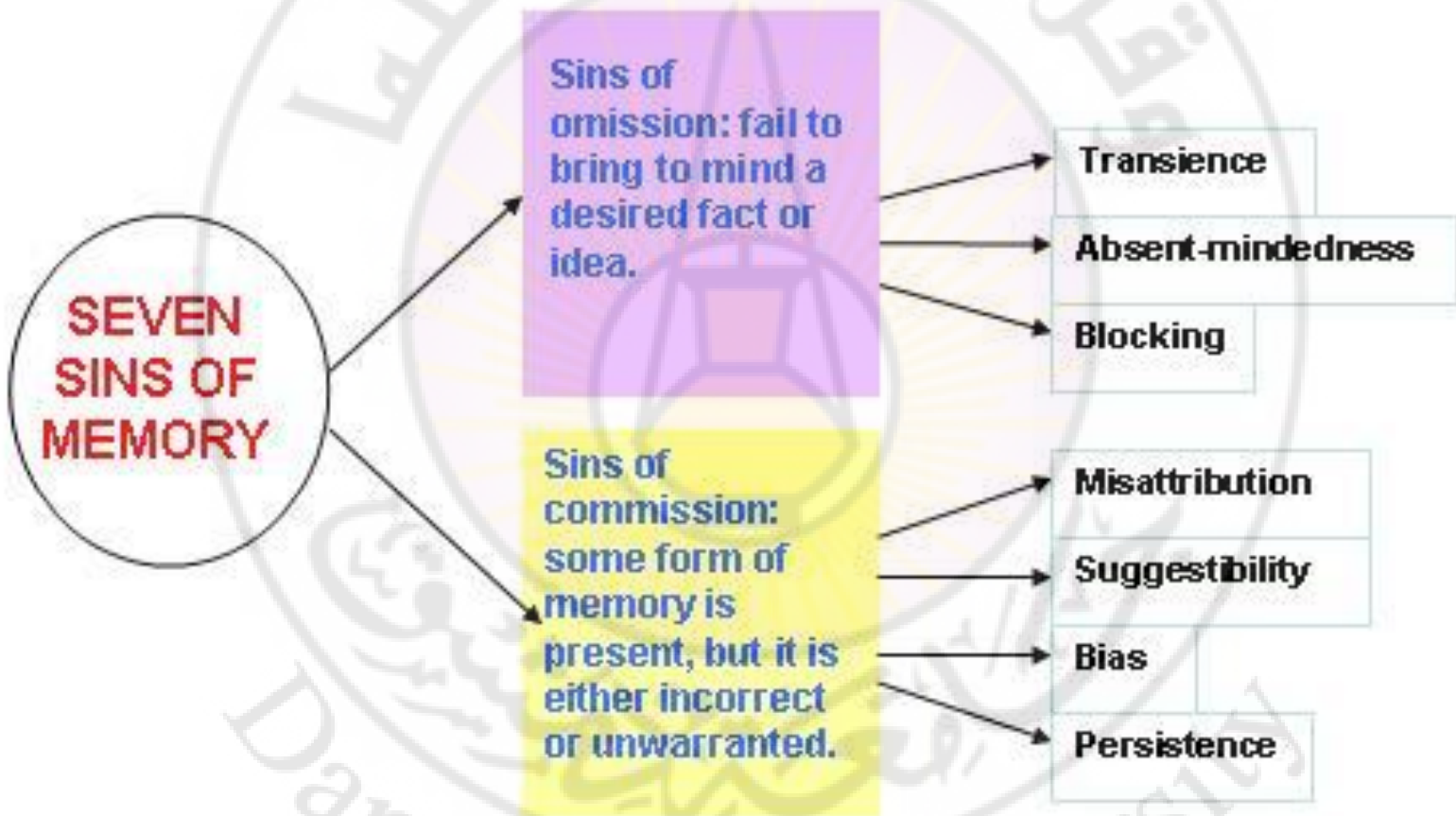
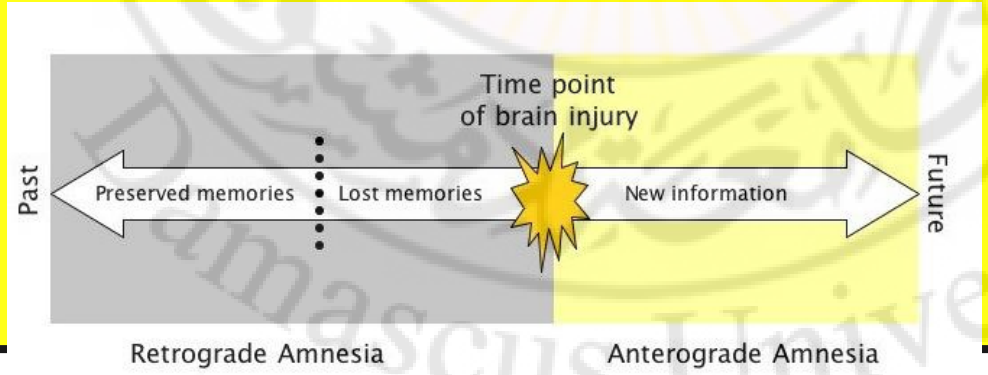
Someone asks you a question and the answer is right on the tip of your tongue

when you retrieve a memory, your mood and other biases at that moment can influence what information you actually recall


SEVEN SINS OF MEMORY
Sins of omission: fail to bring to mind a desired fact or idea.
Transience
Absent-mindedness
Blocking
Sins of commission: some form of memory is present, but it is either incorrect or unwarranted.
Misattribution
Suggestibility
Bias
Persistence

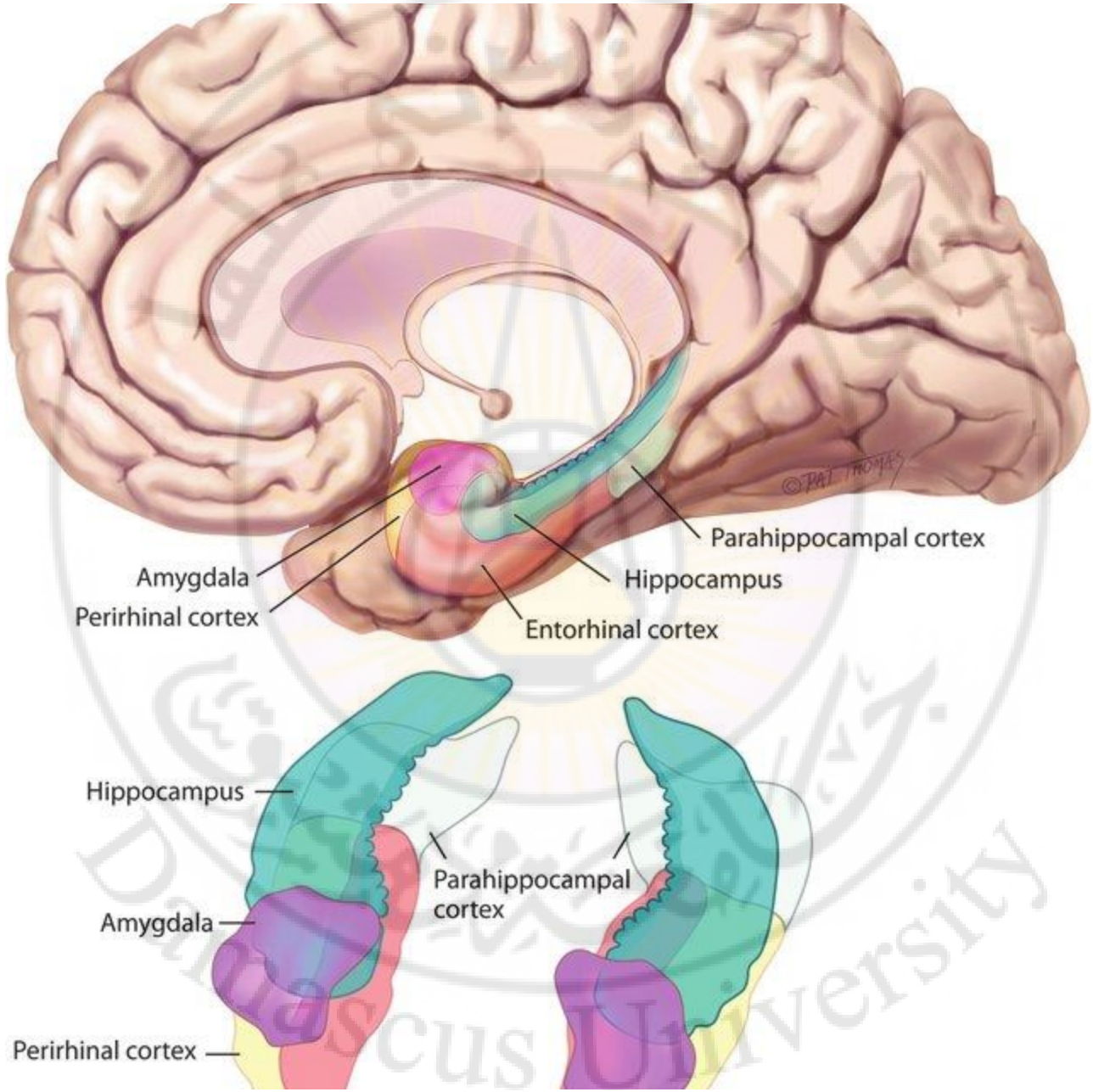
النساوة أو فقد الذاكرة
Amnesia

- تكون جزئية أو كاملة
- مؤقتة أو دائمة
- لها نوعين:
  - نساوة لاحقة: عدم القدرة على ارسال المعلومات من الذاكرة القصيرة إلى الذاكرة الطويلة الأمد
  - نساوة سابقة: عدم القدرة على استحضار معلومات مكتسبة قبل وقت الاصابة وتعود لعدة أشهر أو سنوات للوراء



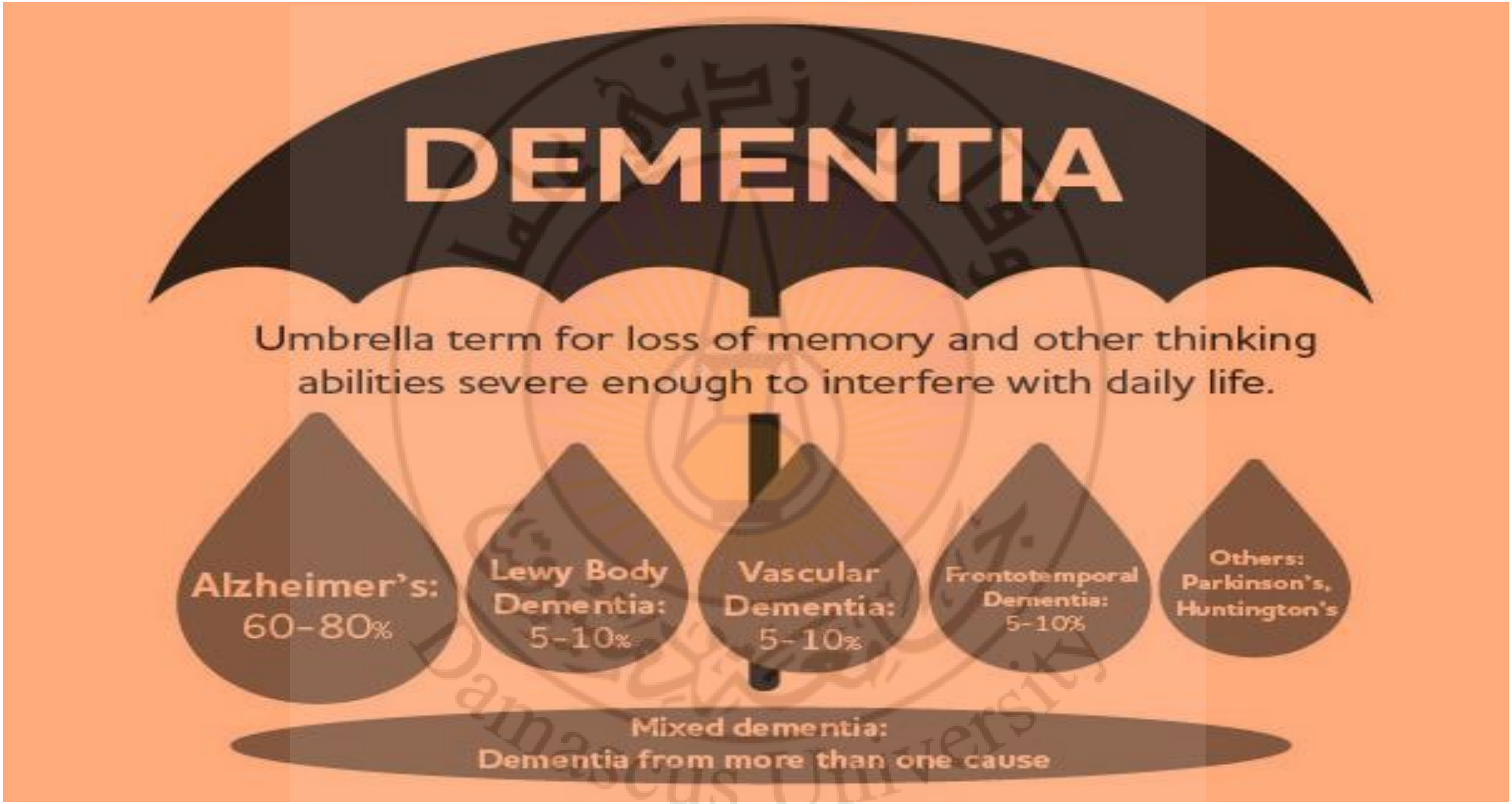
النساوة اللاحقة
Anterograde amnesia

- عدم القدرة على خلق ذاكرة جديدة بسبب أذية الدماغ في حين الذاكرة البعيدة التي سبقت الحدث المؤذي طبيعية
- الأسباب
  - الكحولية المزمنة
  - سوء التغذية الشديد
  - الفالج
  - النزف تحت العنكبوت
  - الرضوض على الرأس
  - متلازمة فيرنيكة كورساكوف
  - نقص الأكسجة
- تنتج عن اصابة الفص الصدغي الأنسي والدماغ البيني الأنسي
- لا يوجد أدوية تفيد في علاج هذا النوع من النساوة


Parahippocampal cortex
Amygdala
Hippocampus
Perirhinal cortex
Entorhinal cortex
Hippocampus
Parahippocampal cortex
Amygdala
Perirhinal cortex

النساوة السابقة
Retrograde amnesia

- عدم القدرة على احضار الذكريات التي سبقت الأذية ولكن بإمكانه احداث ذكريات جديدة
- الأسباب
  - الرضوض الدماغية
  - الفالج
  - الأورام
  - نقص الأكسجة
  - التهاب الدماغ
  - الكحولية المزمنة
- تنتج عن اصابة حصين البحر hippocampus وهو المسئول عن الترميز وتصاب الذاكرة العارضة episodic memory أكثر من الذاكرة الدلالية semantic memory
- المريض يتذكر المعلومات العامة أكثر من المعلومات النوعية وهو قادر على تذكر الذكريات القديمة (المدعمة) أكثر من الحديثة
- عادة النساوة السابقة مؤقتة وتعالج بالتعرض للذكريات الضائعة


DEMENTIA
Umbrella term for loss of memory and other thinking abilities severe enough to interfere with daily life.
Alzheimer's: 60–80%
Lewy Body Dementia: 5–10%
Vascular Dementia: 5–10%
Frontotemporal Dementia: 5–10%
Others: Parkinson's, Huntington's
Mixed dementia: Dementia from more than one cause

Cortial & Subcortical

CORTICAL

Alzheimer's
Frontotemporal
Binswanger's
Creutzfeldt-Jakob

SUBCORTICAL

Parkinson's
Huntington's
AIDS/HIV Dementia

Primary & Secondary

PRIMARY

Alzheimer's
Vascular Dementia

SECONDARY

Brain Infections
Supranuclear Palsy
Multiple Sclerosis

Reversible & Irreversible

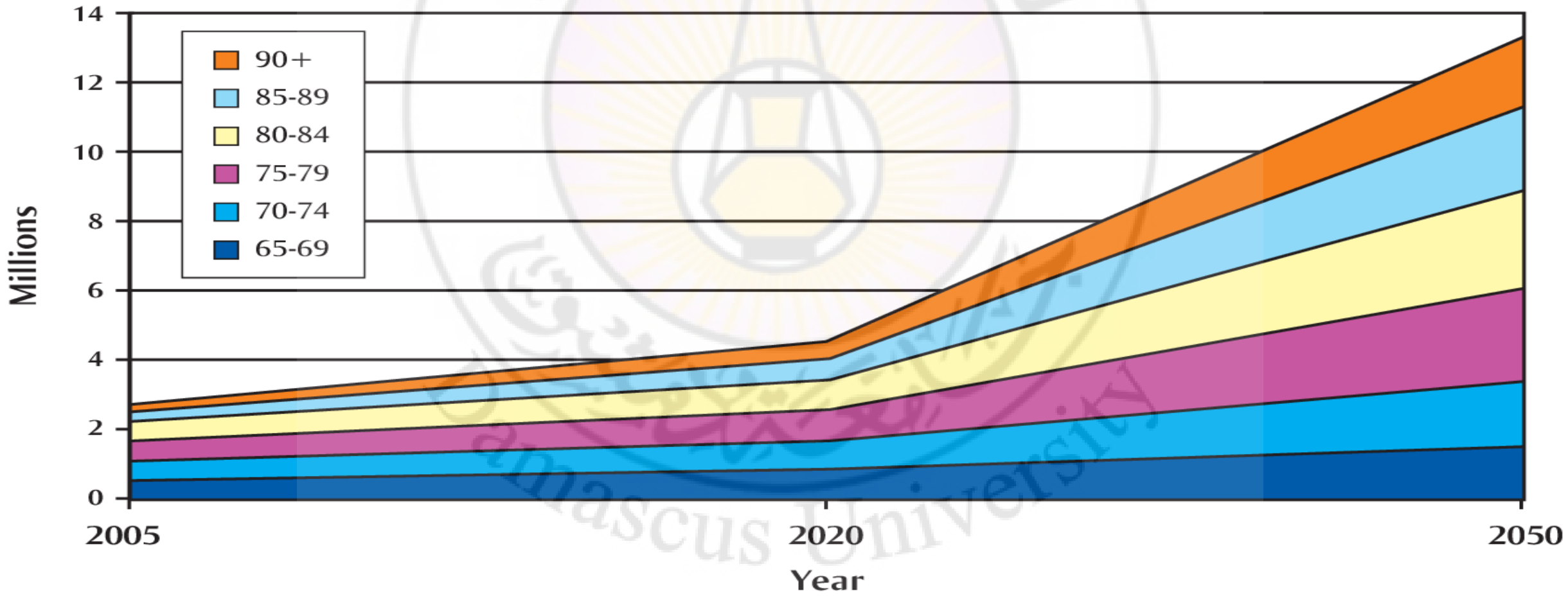
REVERSIBLE

Responsive to Treatment
Temporary Condition
Likely from Secondary Cause or Environmental Factors

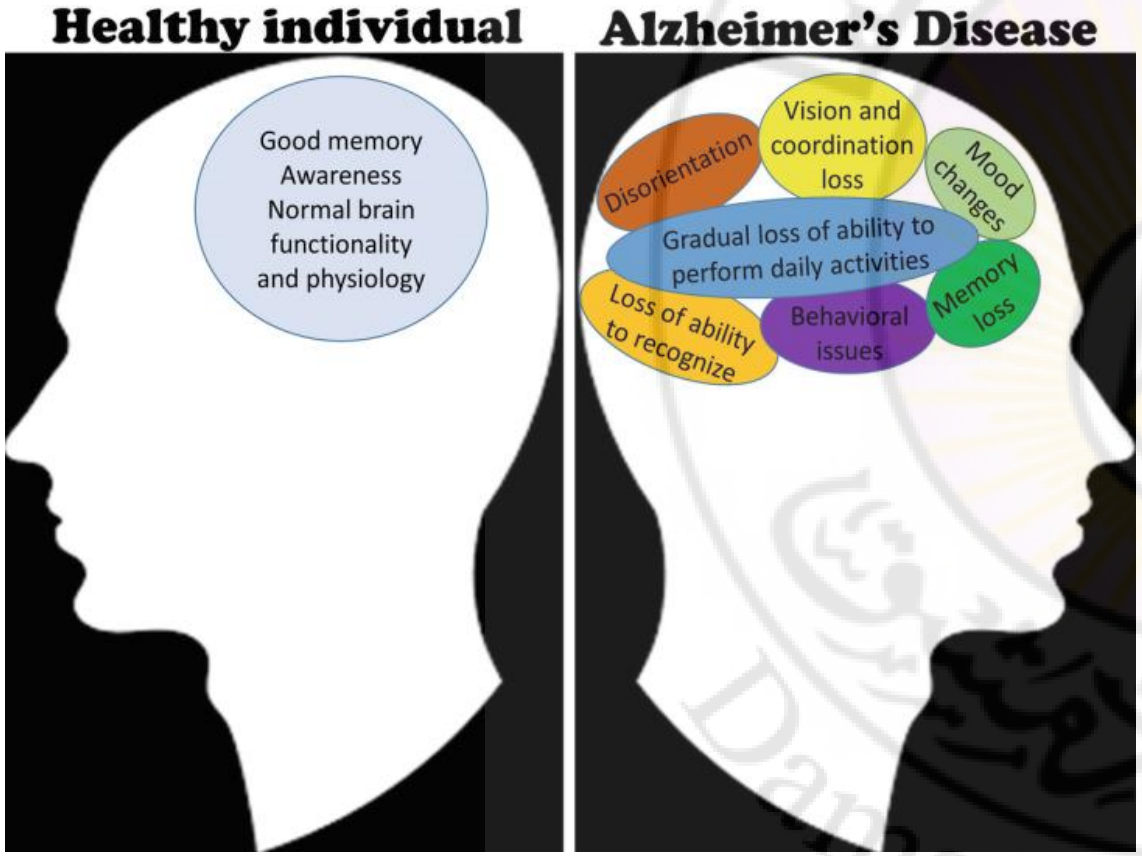
IRREVERSIBLE

Progressive & Incurable
Permanent Brain Damage
Can be from Primary or Secondary Conditions

Trend in Dementia incidence by age over time (2005-2050).

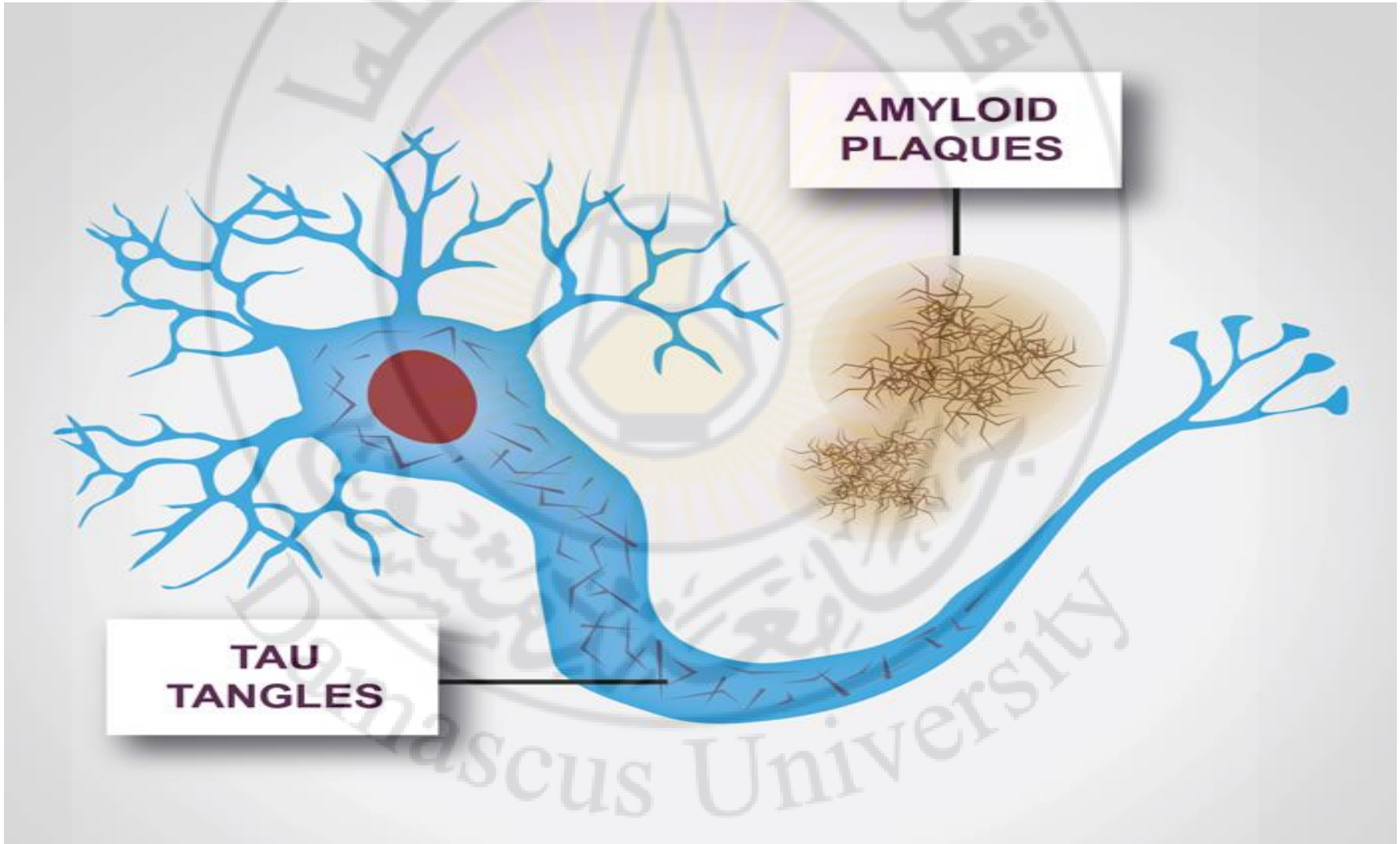


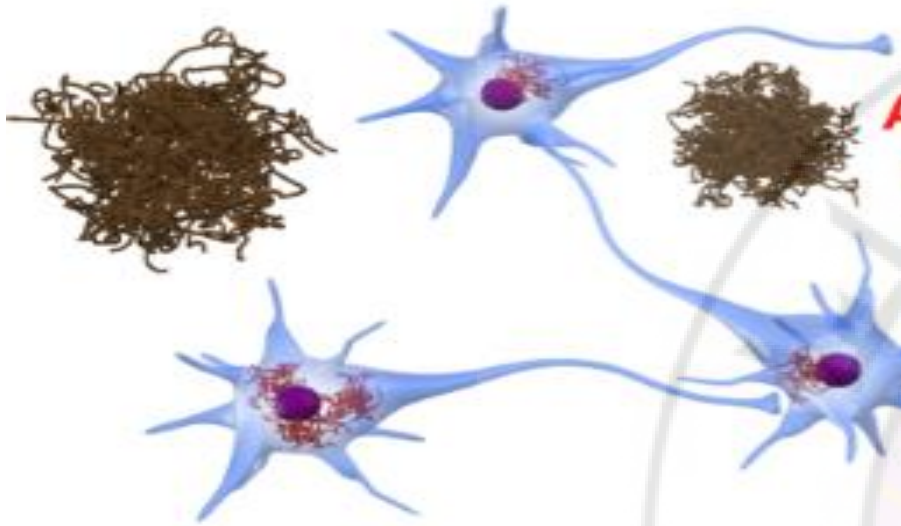
خرف الزهايمر Alzheimer



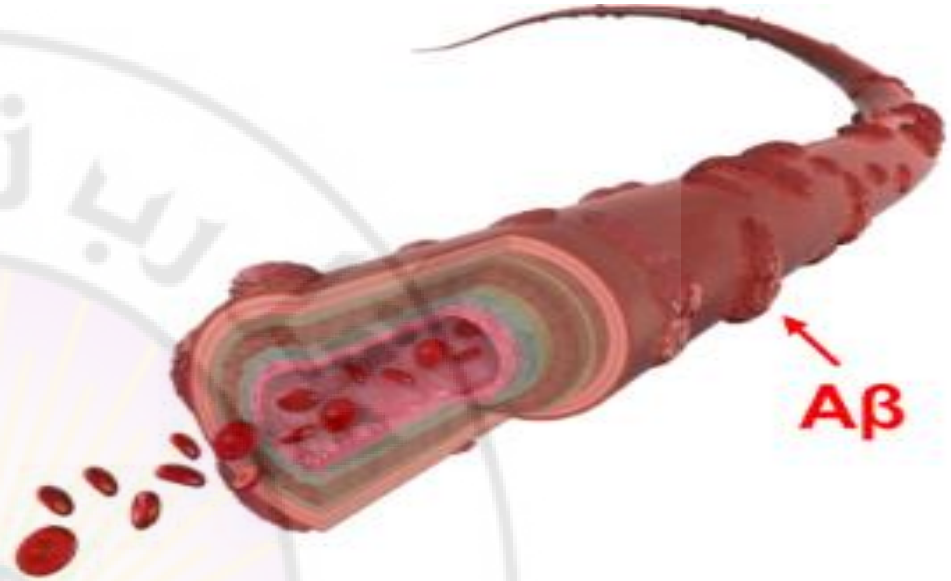
- تتأثر الذاكرة أولا
- اللغة ثانية
- اضطرابات الحيز
- البصيرة والمحاكمة يصابان بشكل متأخر
- الاصابة الرئيسة في الناحية الصدغية والجدارية

Alzheimer’s disease is characterized by both deposit of an extracellular protein, beta-amyloid (or Abeta), which leads to the formation of beta-amyloid plaques, and by abnormal function of the Tau protein.





Amyloid plaque



Aβ

Parenchymal Aβ accumulation
(senile plaque)

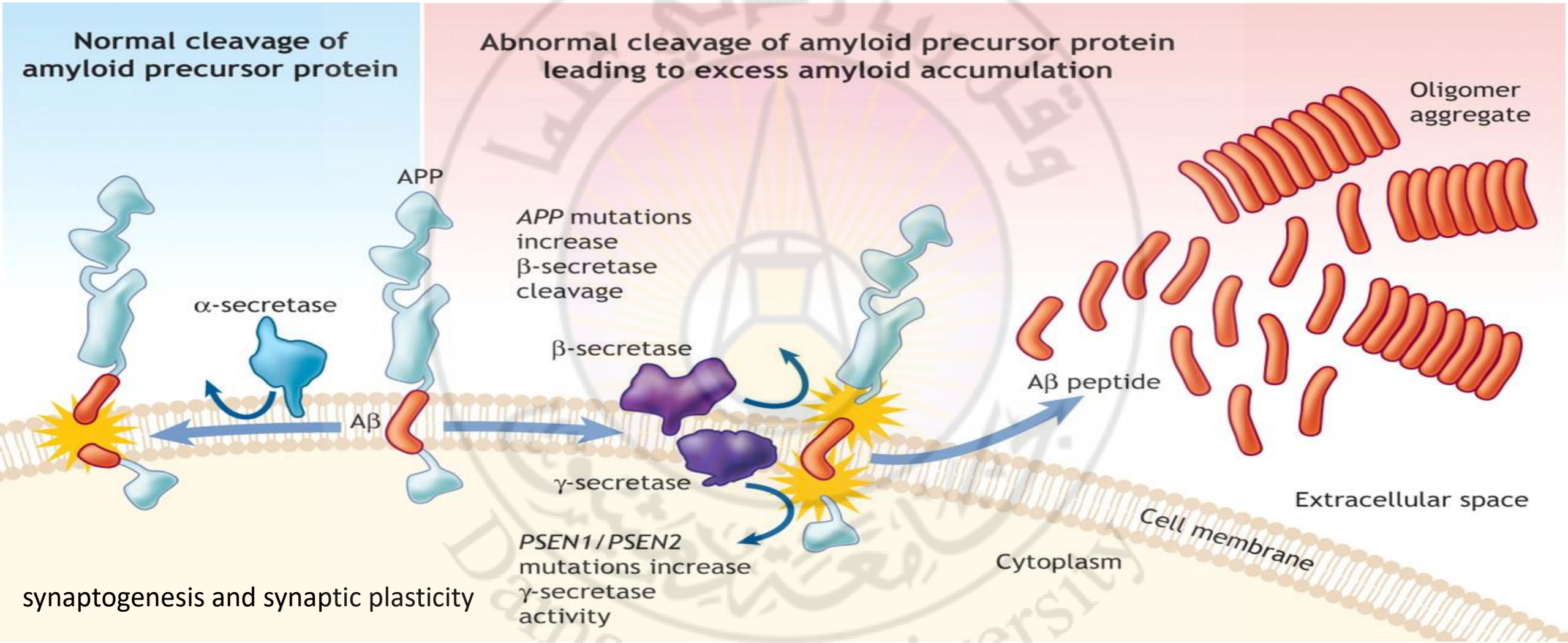
Vascular Aβ accumulation
(cerebral amyloid angiopathy)

Aβ

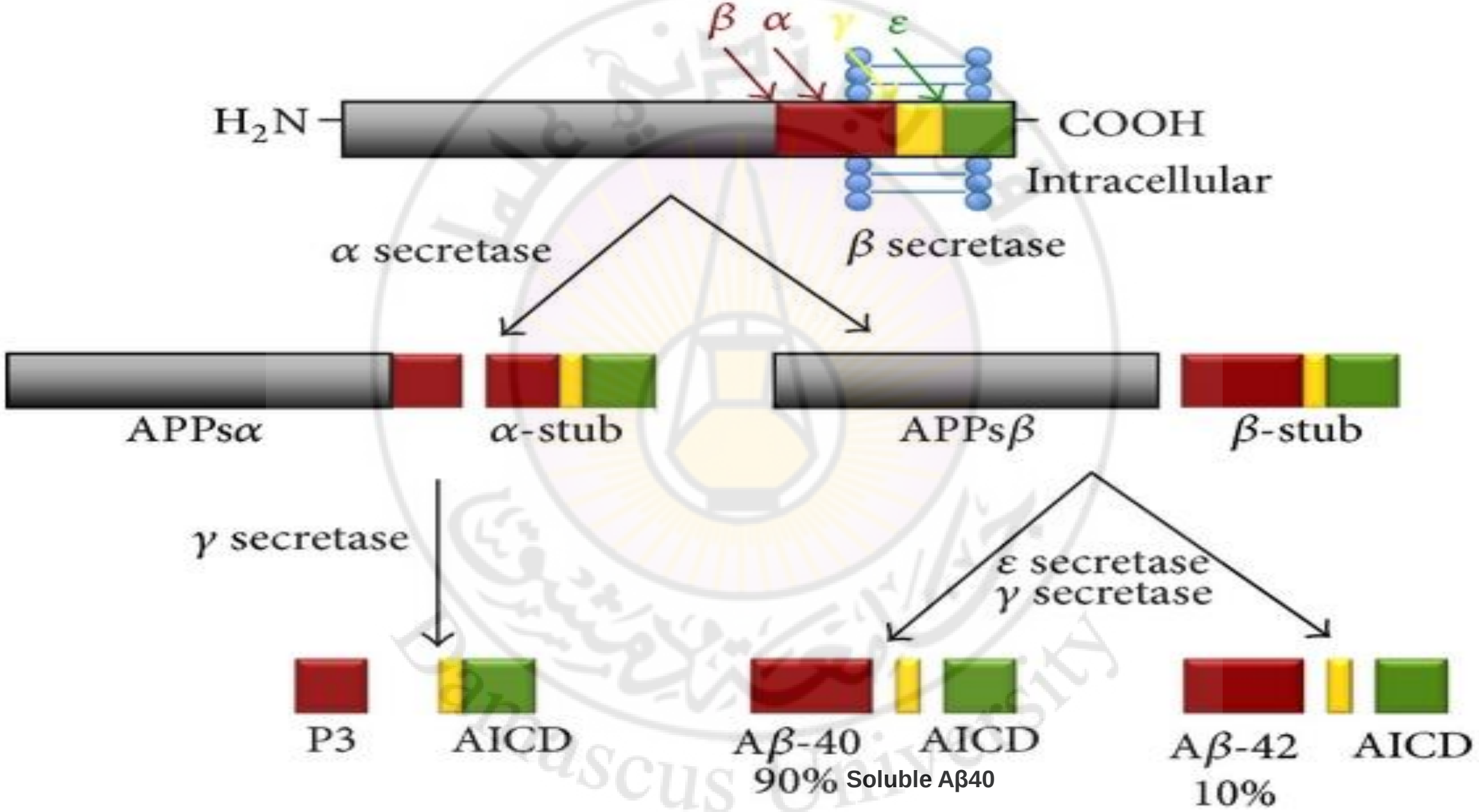
Alzheimer's disease

Cerebrovascular damage

Cognitive impairment

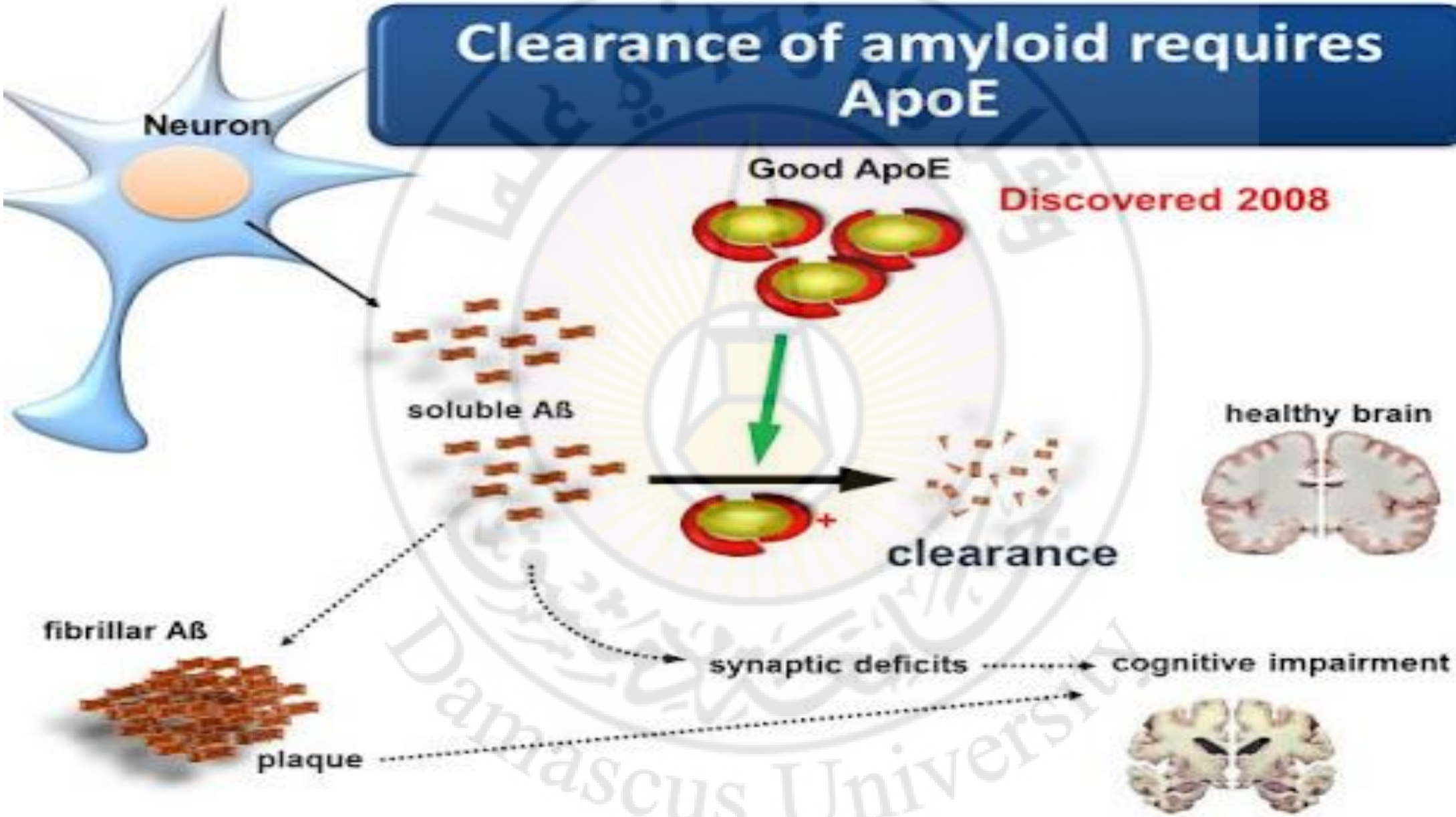


synaptogenesis and synaptic plasticity

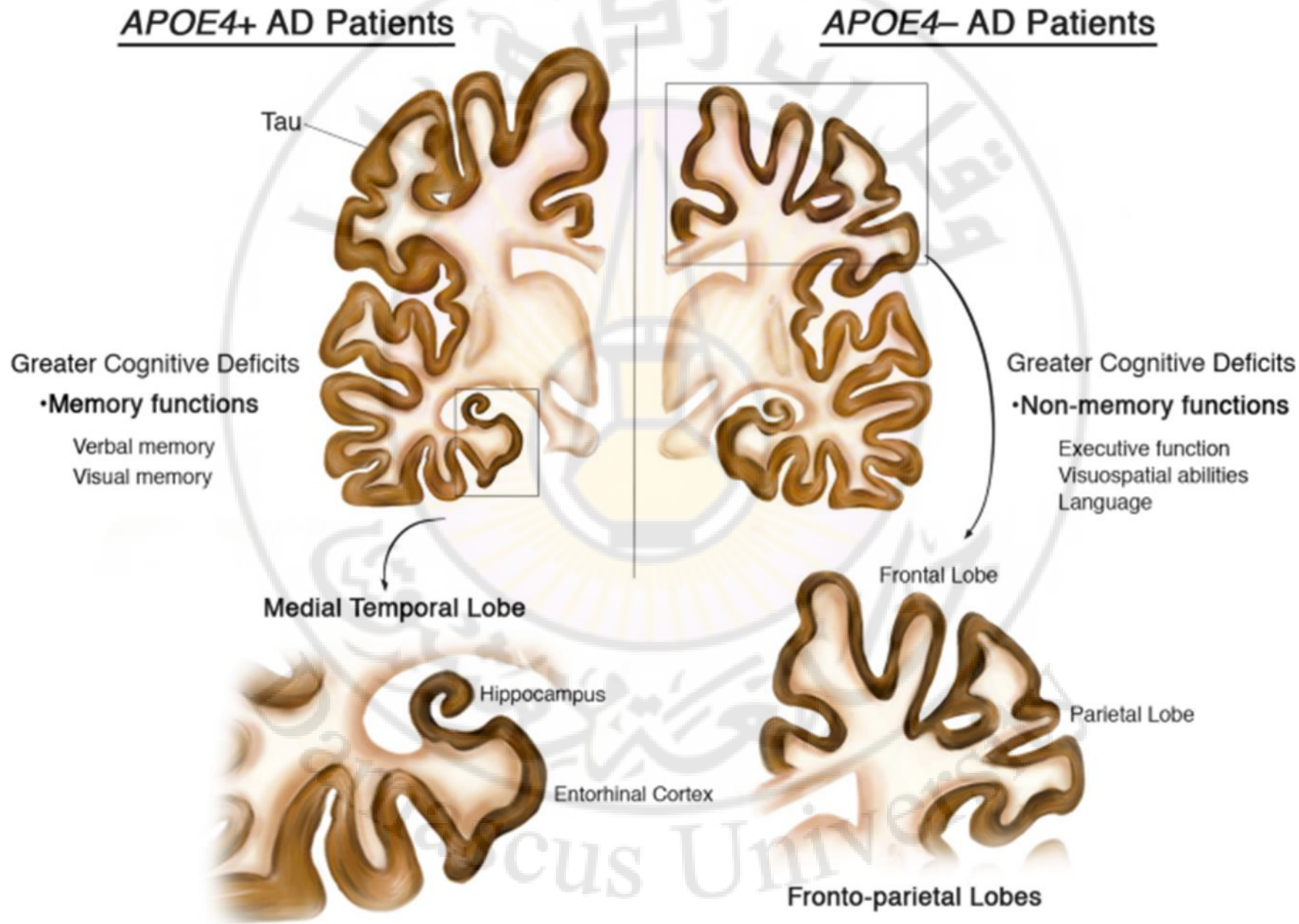


Amyloid plaques contain both Aβ40 and Aβ42,while vascular amyloid is predominantly the shorter Aβ40

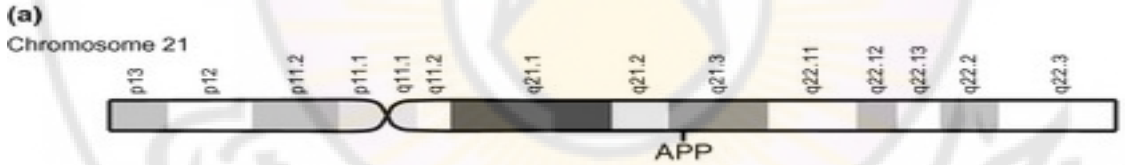
Clearance of amyloid requires ApoE

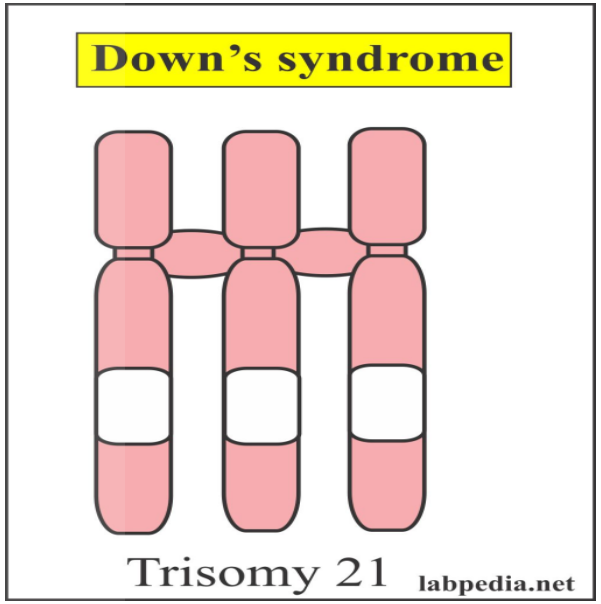


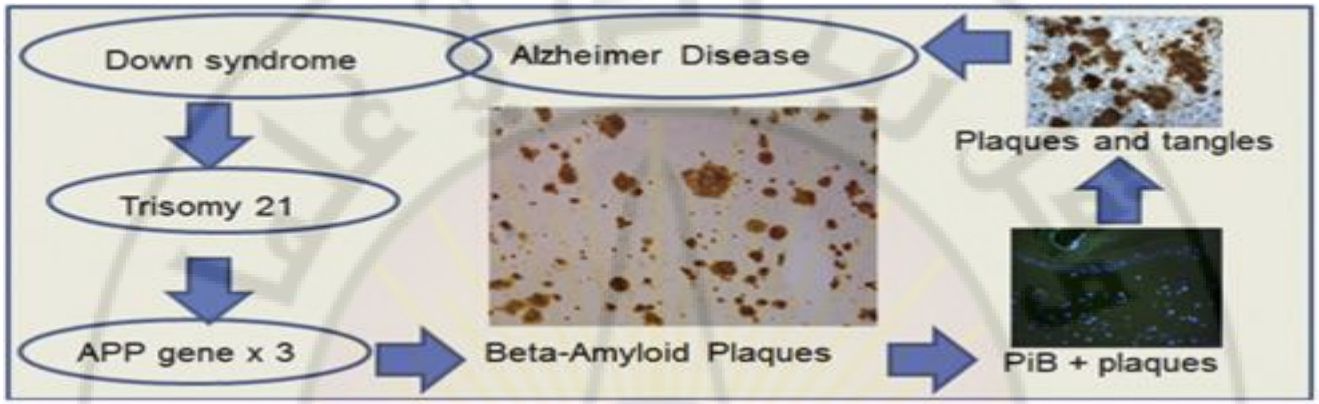
APOE4-associated Alzheimer's Disease Heterogeneity



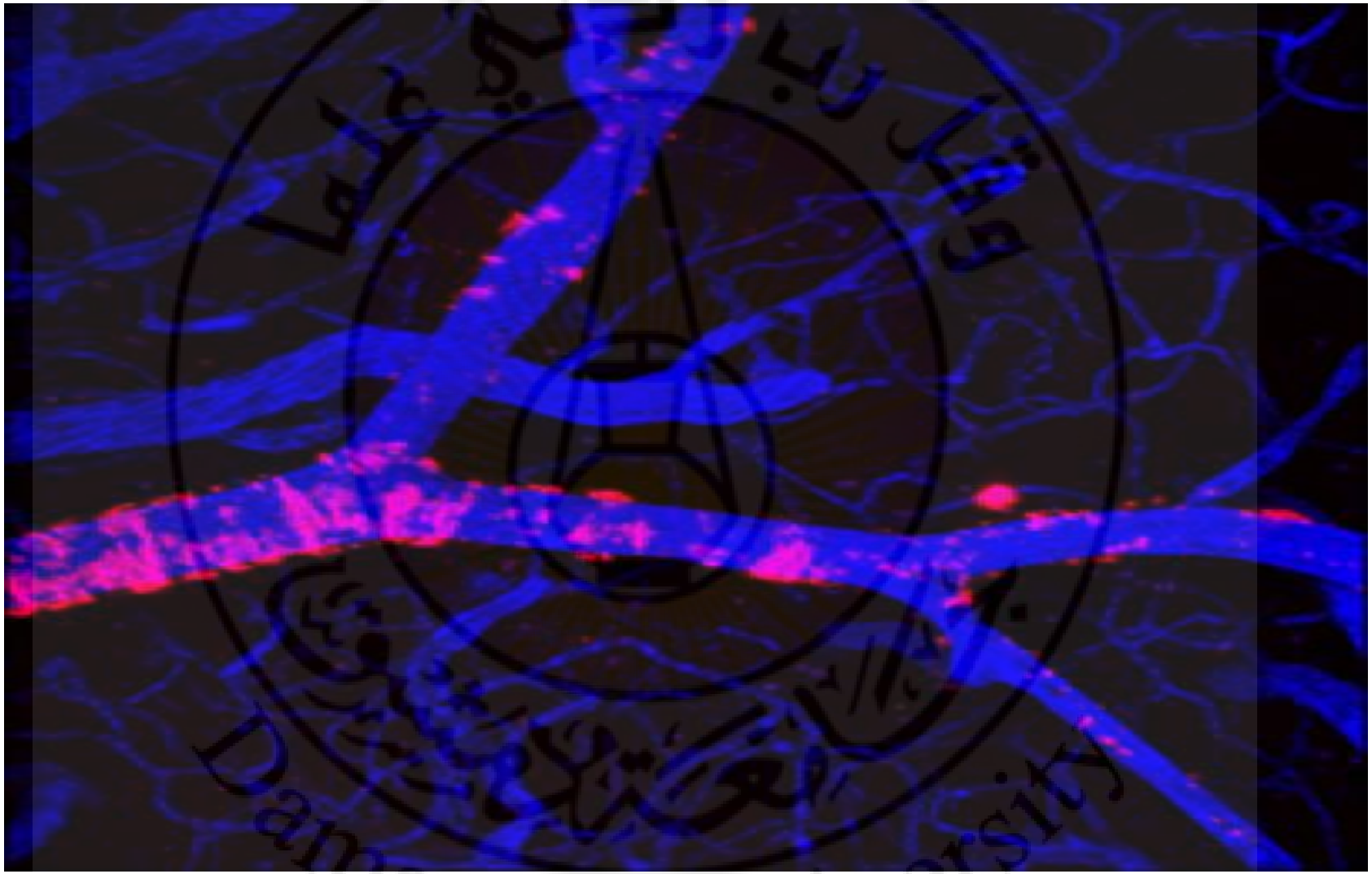
In 1991, the *amyloid hypothesis* postulated that extracellular beta-amyloid (A_β) deposits are the fundamental cause of the disease. Support for this postulate comes from the location of the gene for the amyloid precursor protein (APP) on chromosome 21, together with the fact that people with trisomy 21 (**Down Syndrome**) who have an extra gene copy almost universally exhibit AD by 40 years of age





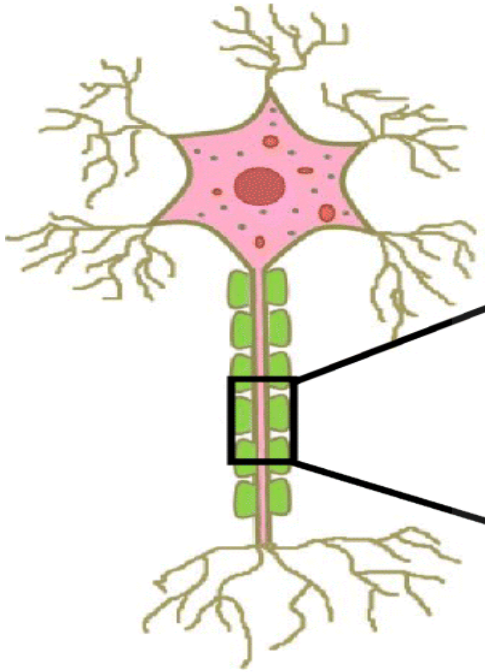

Down syndrome
Alzheimer Disease
Trisomy 21
APP gene x 3
Beta-Amyloid Plaques
Plaques and tangles
PiB + plaques

Additional in Alzheimer's disease

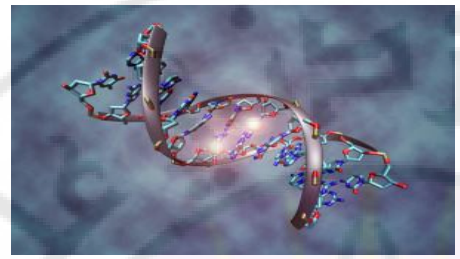


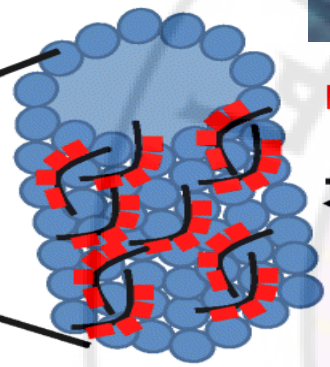
Cerebral amyloid angiopathy (CAA)

Pathophysiology of Tau in Alzheimer's Disease



Healthy Neuron

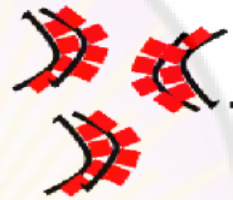




Microtubules
Stabilized by Tau

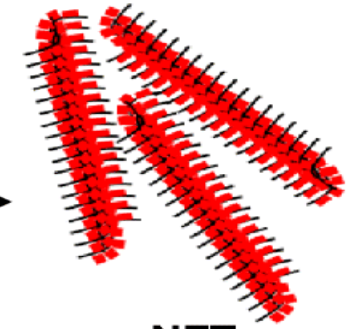
Phosphorylation and
Oxidative Stress

Phosphatases and
Chaperones

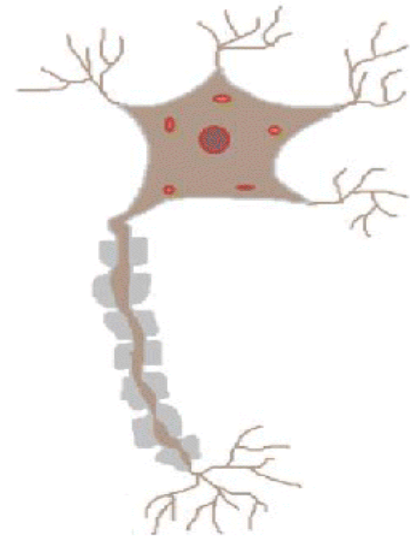


Dimer

Oligomer



NFTs



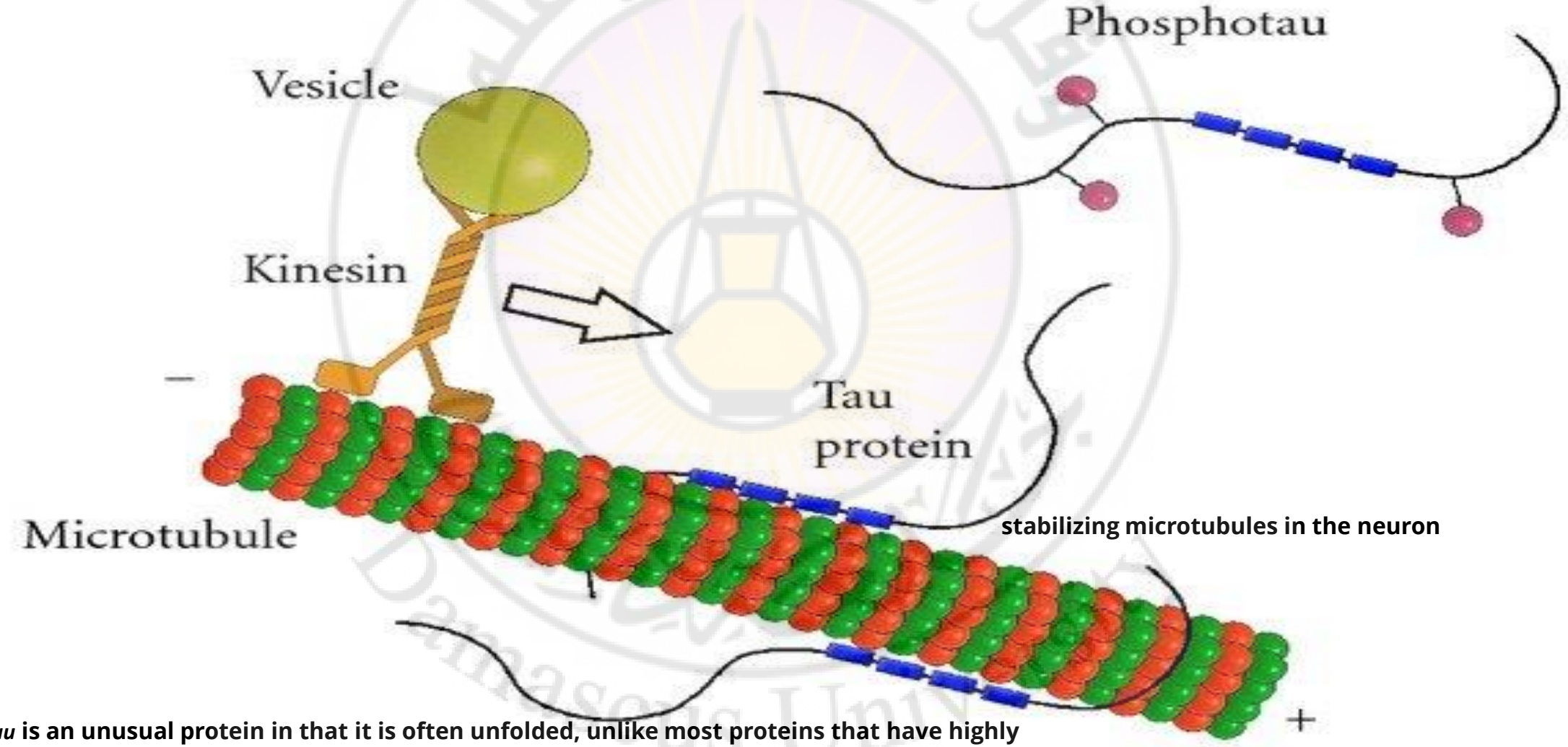
Degenerated Neuron

Tubulin Dimer

Tau

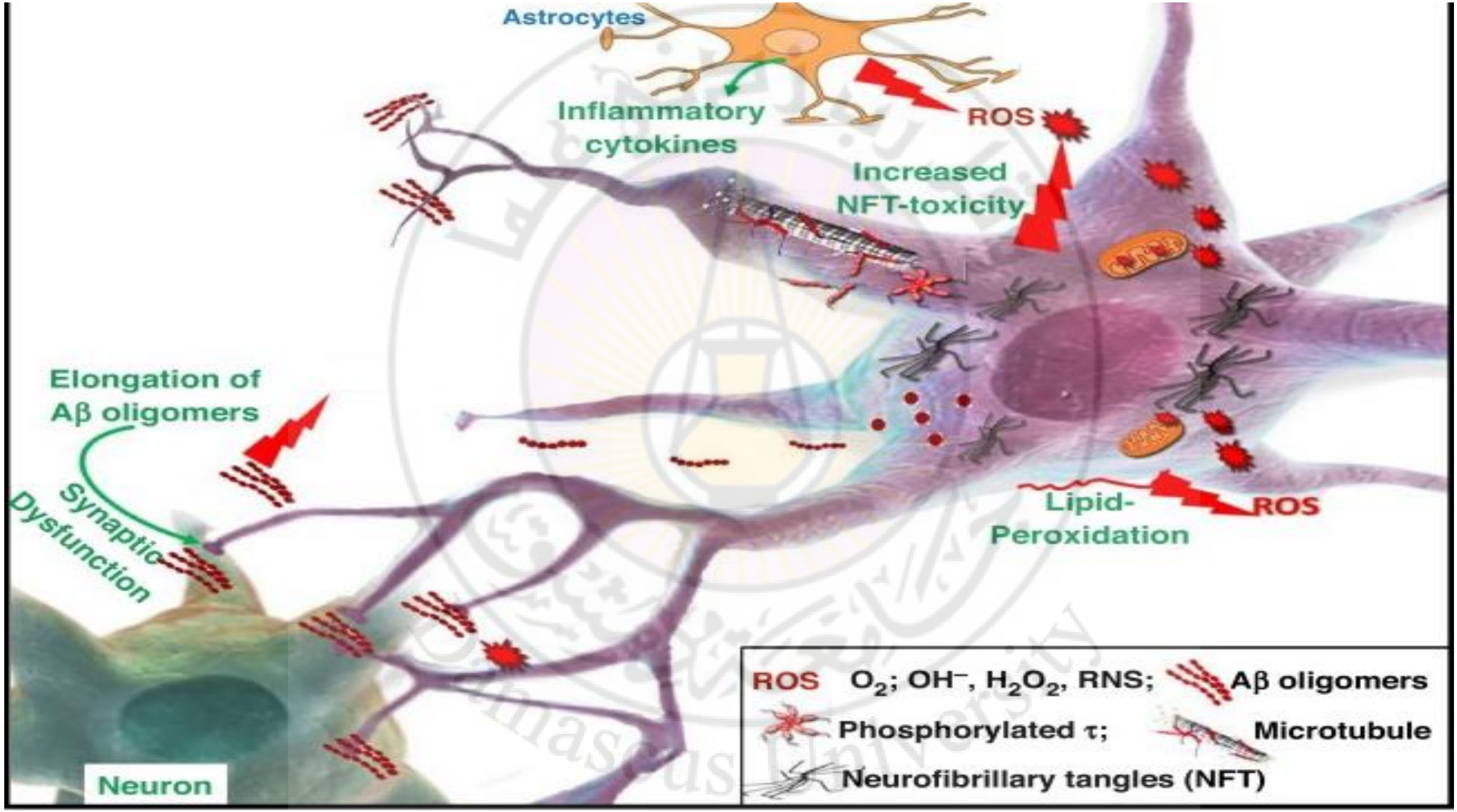
NFTs- Neurofibrillary Tangles

Tau protein stabilizes microtubules through four tubulin binding domains (blue boxes) in case of the longest isoform.



stabilizing microtubules in the neuron

Tau **is an unusual protein in that it is often unfolded, unlike most proteins that have highly specific shapes determining their functions**


Astrocytes
Inflammatory cytokines
ROS
Increased NFT-toxicity
Elongation of Aβ oligomers
Synaptic Dysfunction
Lipid-Peroxidation
ROS
Neuron
ROS O_2; OH^-, H_2O_2, RNS;
Aβ oligomers
Phosphorylated τ;
Microtubule
Neurofibrillary tangles (NFT)

خرف داء لوي المنتشر
Lewy Body Dementia

- أولى الأعراض تدني القدرات الاستعرافية وتتجلى خاصة بالقدرة على الوظيفة التنفيذي فلا يقدر الشخص على التخطيط أو التحليل أو الفكر التجريدي
- الصحو مضطرب من يوم لآخر وكذلك التيقظ والذاكرة القريبة تعلو وتنخفض
- تظهر اهلاسات بصرية قوية وبتفاصيل واضحة وتكون مستمرة أو مترددة
- كما يظهر اضطراب في دورة النوم مرحلة REM تتجلى بأحلام حية وحركات عنيفة أو هادفة وسقوط من السرير
- باركنسونية

Dementia with Lewy Bodies

Core Features

- Fluctuating cognition
- Recurrent well-formed visual hallucinations
- Spontaneous features of parkinsonism

Suggestive Features

- REM sleep behavior disorder
- Severe neuroleptic sensitivity
- Low dopamine transporter uptake in basal ganglia on SPECT/PET

Supportive Features

- Falls
- Autonomic dysfunction
- Delusions
- Depression

Progression of Lewy Body Dementia

Early Stages

Delusions, restlessness, REM sleep disorder, movement difficulties, urinary issues

Middle Stages

Motor impairment, speech difficulty, decreased attention, paranoia, significant confusion

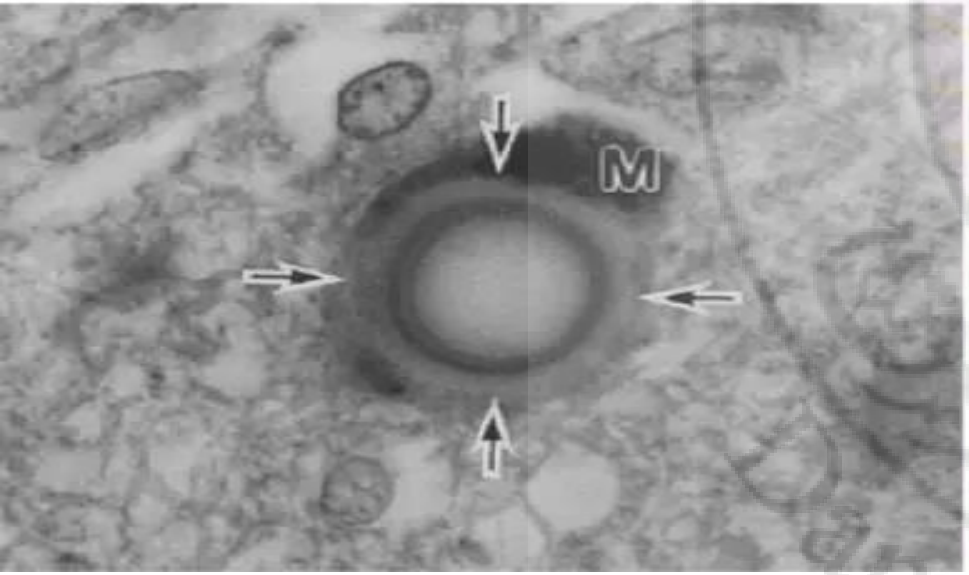
Later Stages

Extreme muscle rigidity and speech difficulties, sensitivity to touch, susceptibility to infections

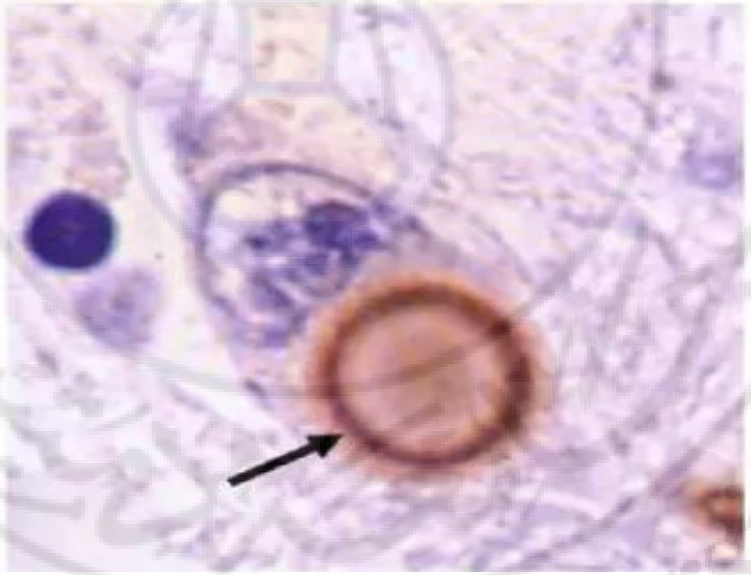
How do Lewy bodies form? And what is their function?

Parkinson's associated proteins like alpha synuclein and SOD1 appear to be present in the periphery of the Lewy body, as opposed to another Parkinson's associated protein, Ubiquitin, which is mainly present in the core of Lewy bodies

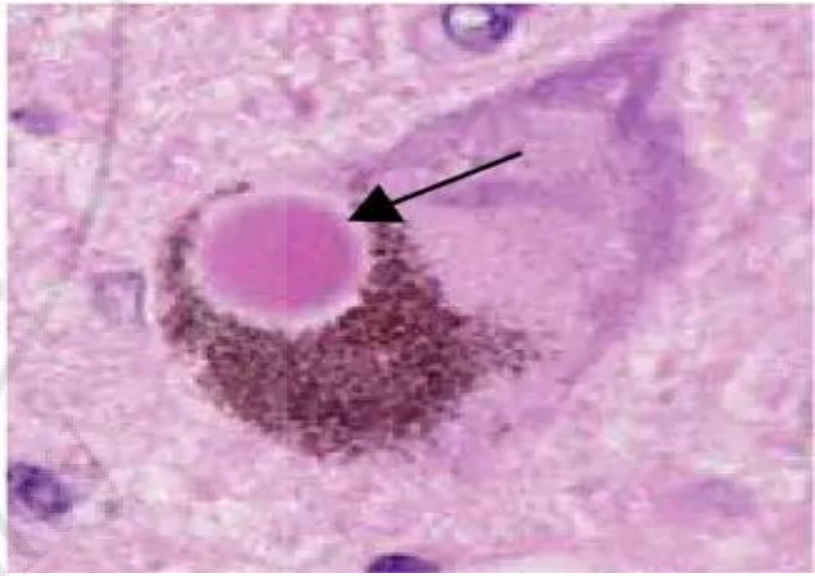
SOD1



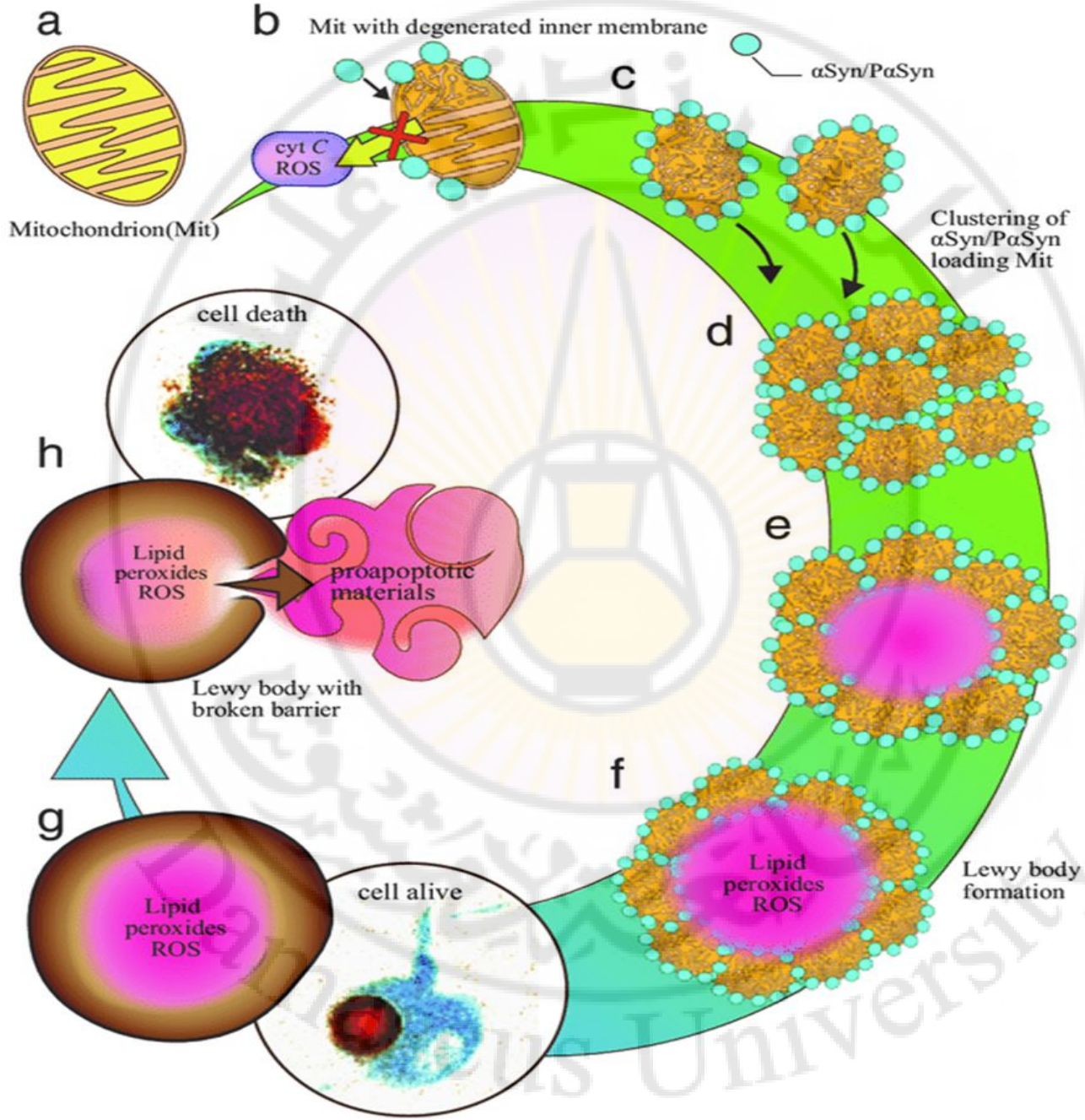
Alpha synuclein



Ubiquitin

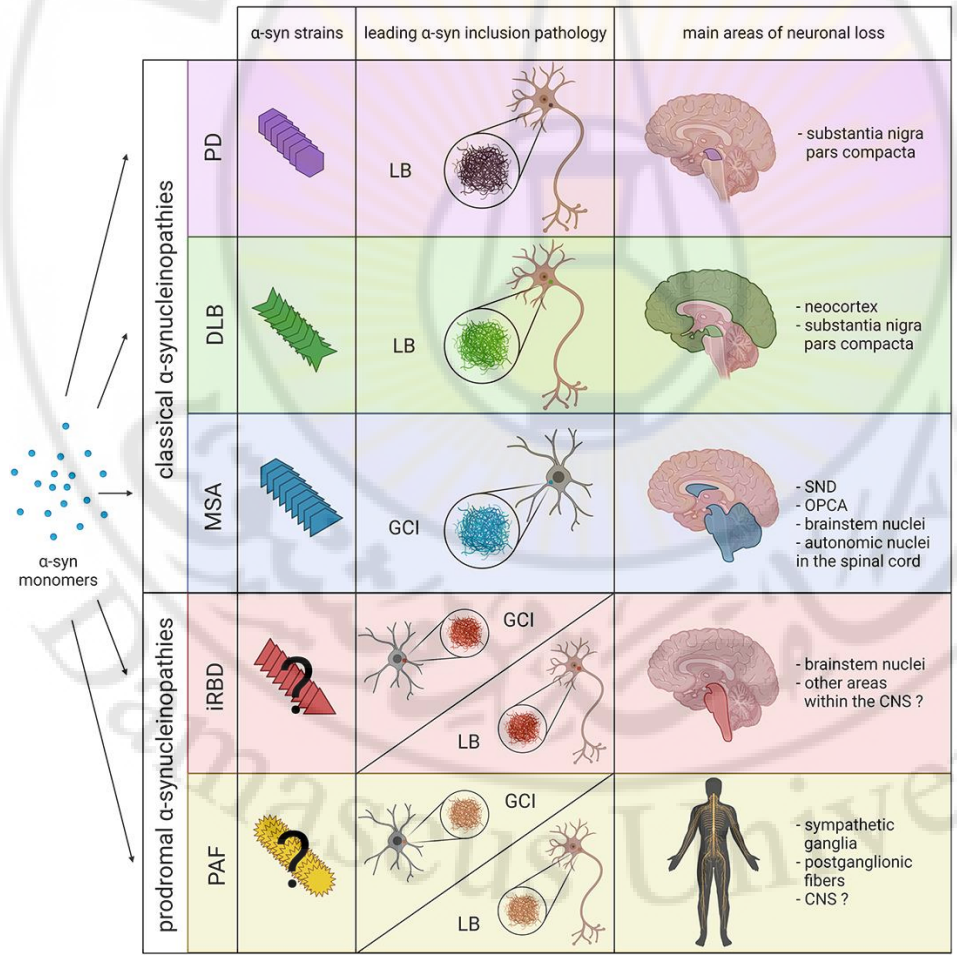


Using different staining techniques at least 90 different molecules have been found in Lewy bodies, so it is wrong to think of them as simply aggregates of alpha synuclein

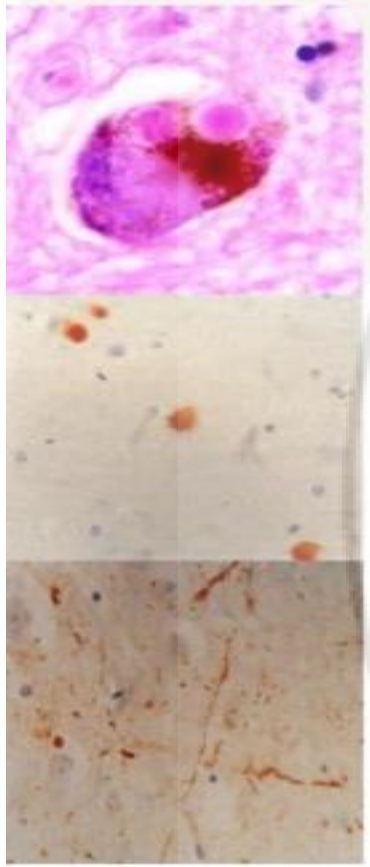

a
b
Mit with degenerated inner membrane
αSyn/PαSyn
c
cyt C
ROS
Mitochondrion(Mit)
Clustering of
αSyn/PαSyn
loading Mit
d
cell death
h
e
Lipid
peroxides
ROS
proapoptotic
materials
Lewy body with
broken barrier
f
g
Lipid
peroxides
ROS
cell alive
Lipid
peroxides
ROS
Lewy body
formation

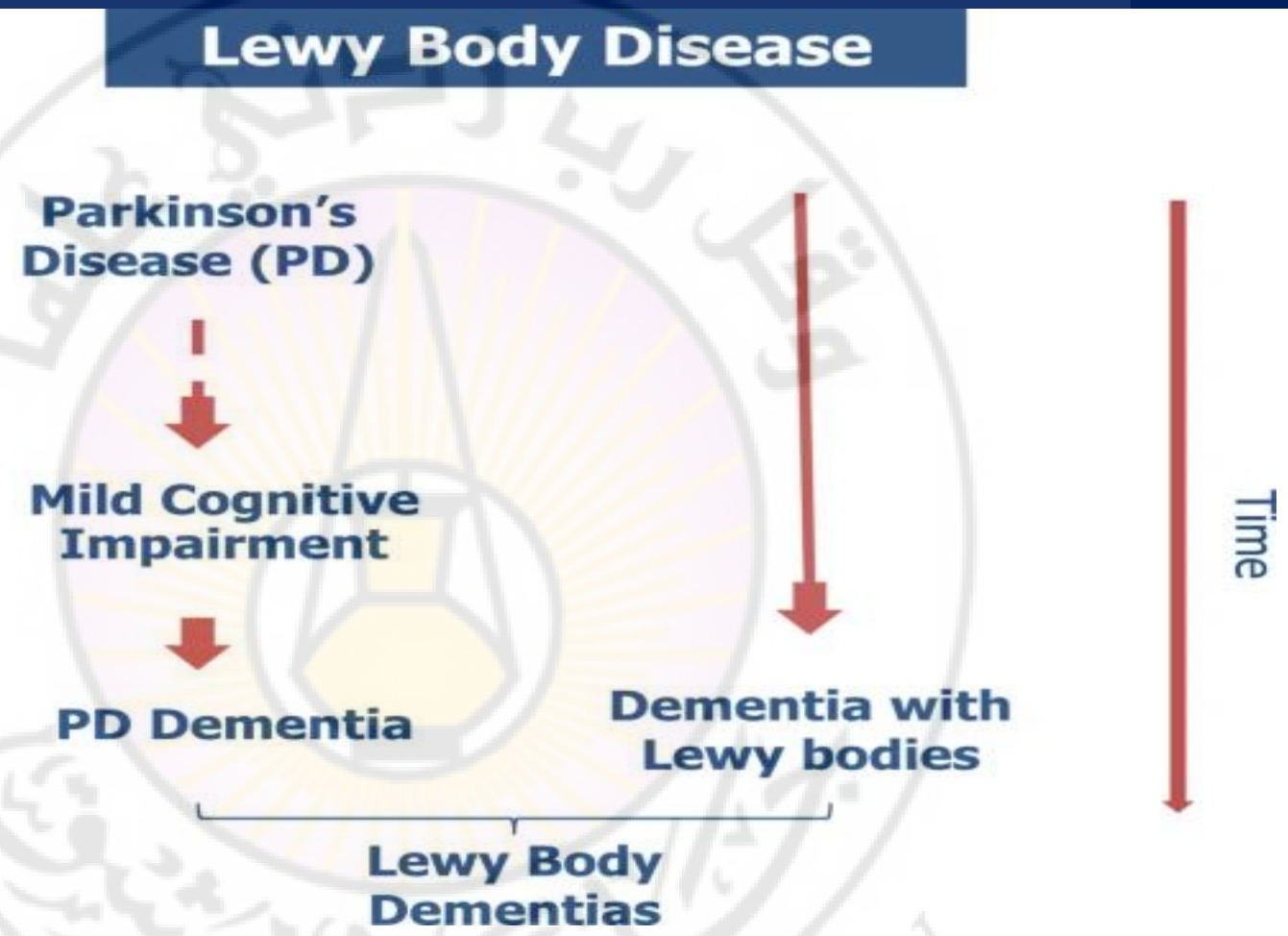
There are three main types of synucleinopathy:

Parkinson's disease (PD),
dementia with Lewy bodies (DLB),
multiple system atrophy (MSA)

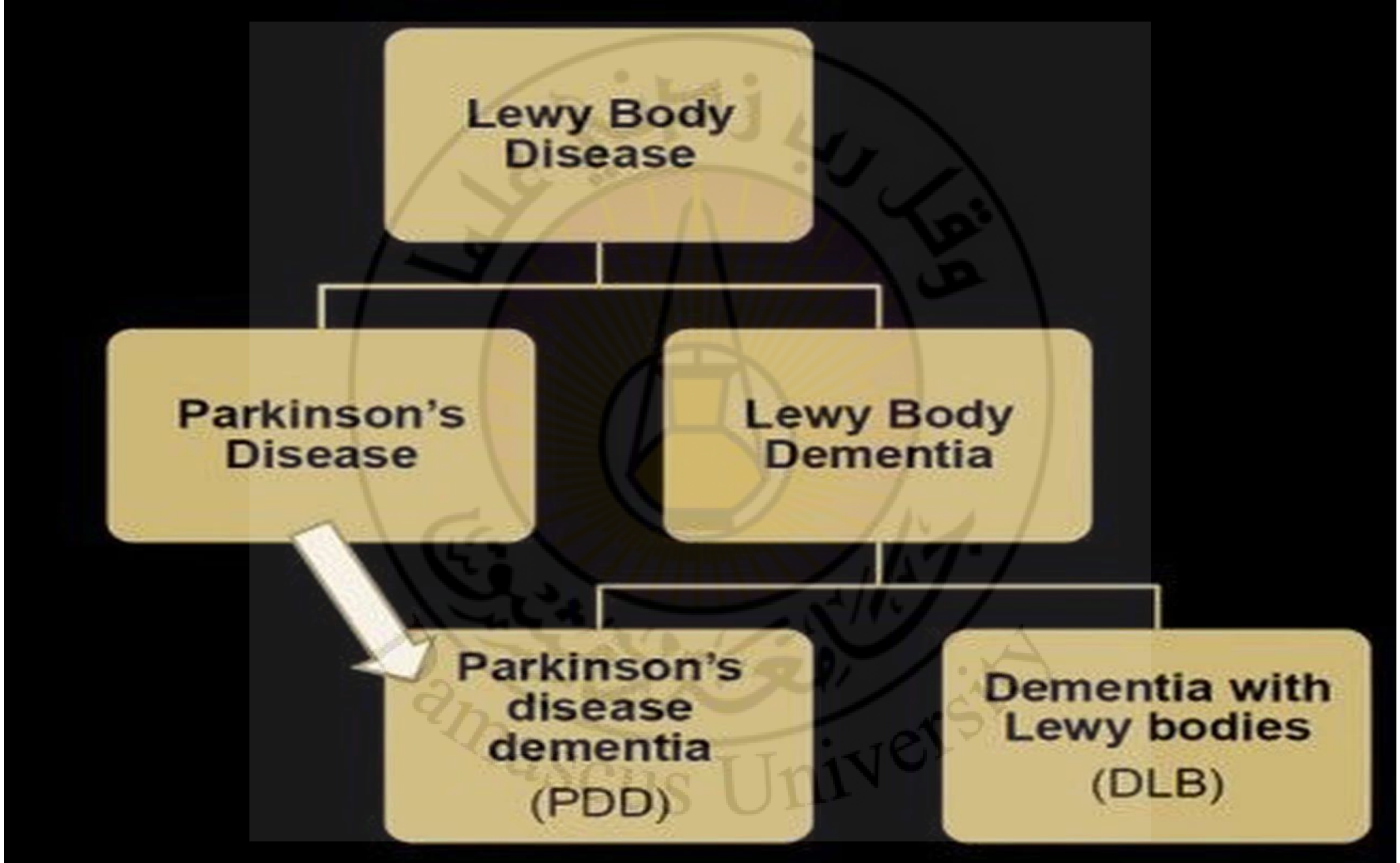


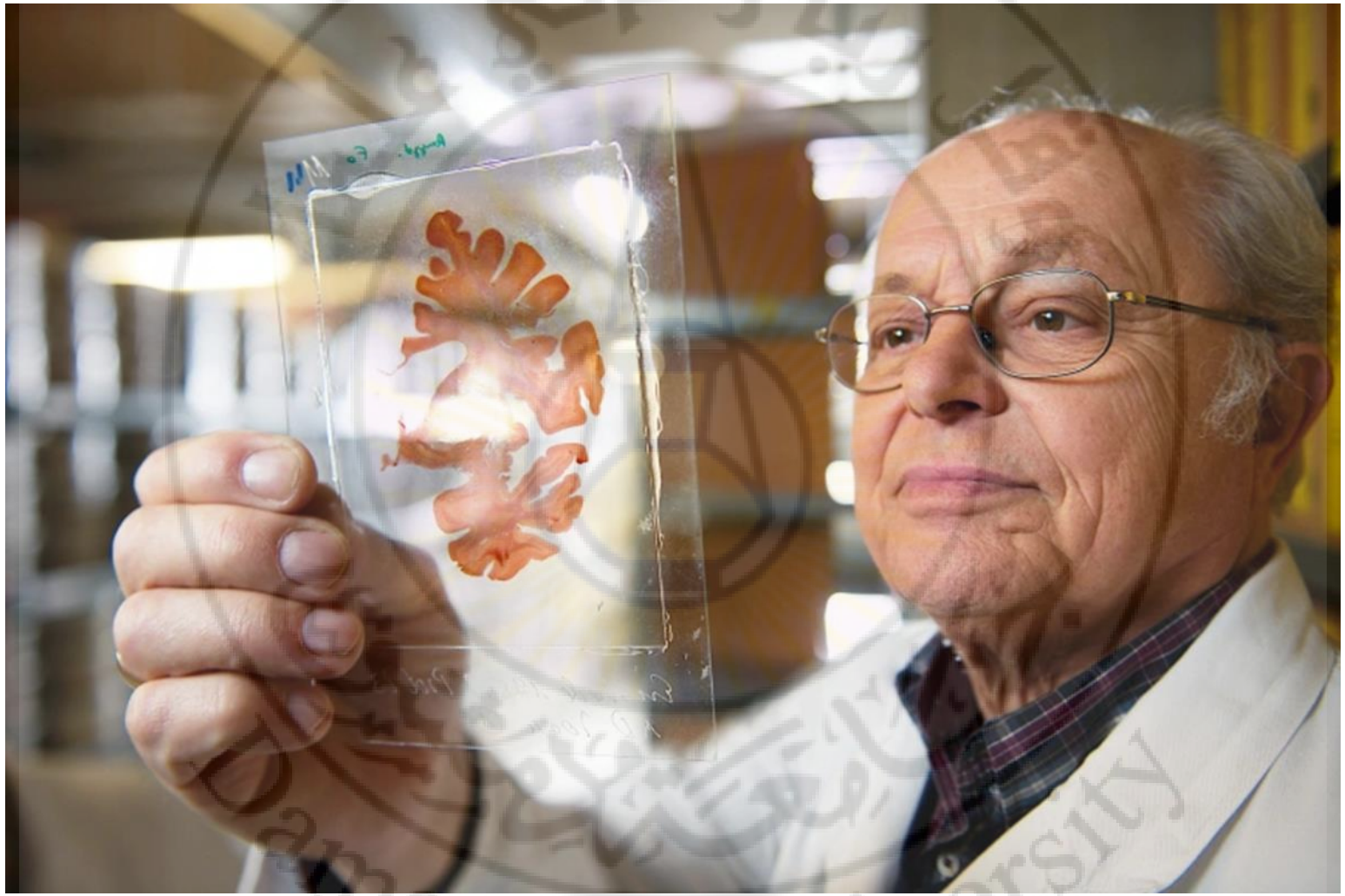
The three disorders can be viewed as existing on a spectrum of LB disease



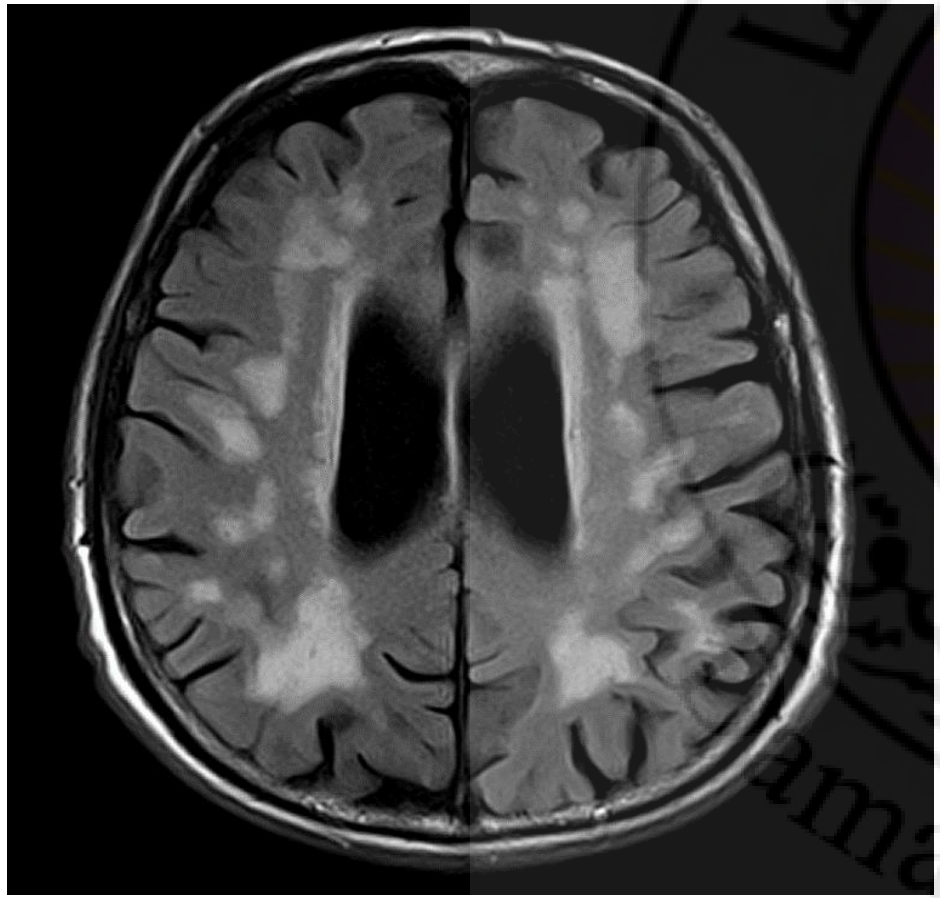


Nomenclature of Lewy body diseases. Parkinson's disease dementia is diagnosed when cognitive impairment develops a year or more after the onset of parkinsonism. Dementia with Lewy bodies is diagnosed when cognitive symptoms appear without parkinsonism or less than 1 year after the onset of parkinsonism.

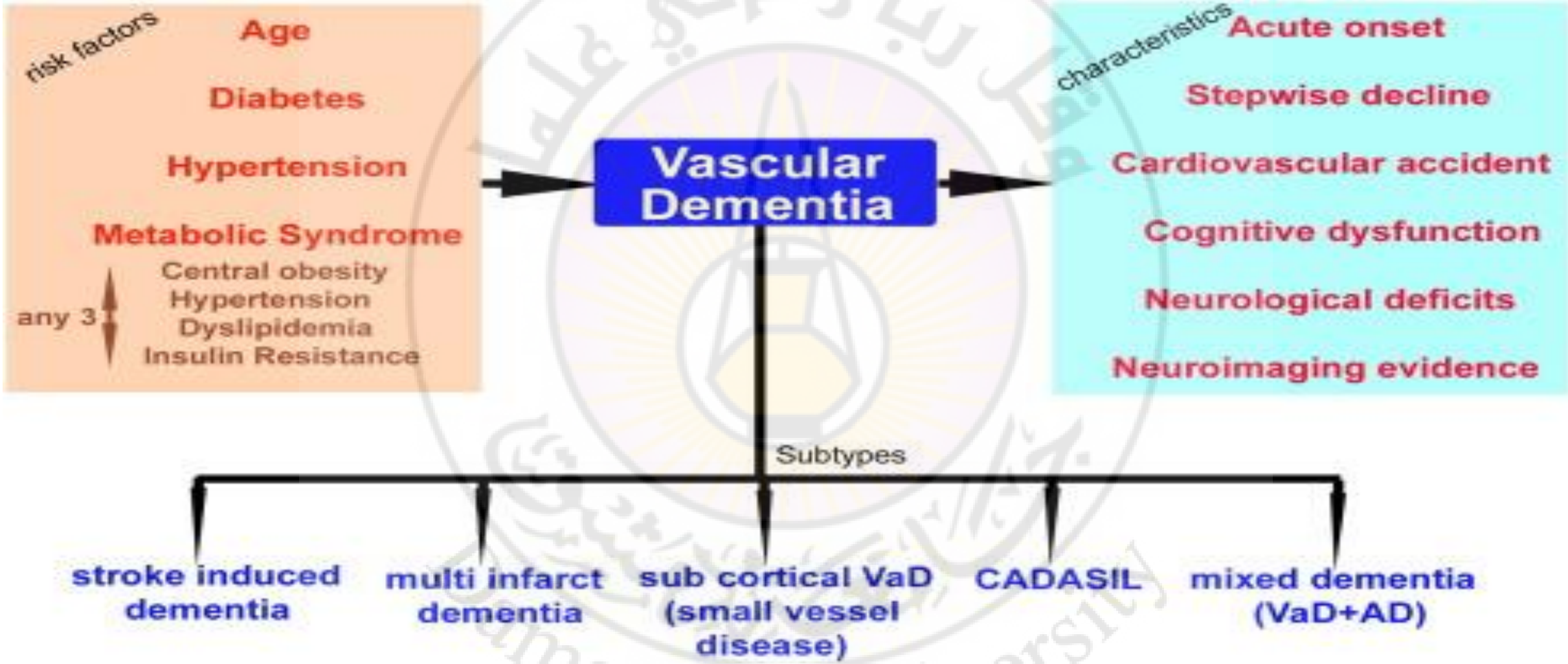

Lewy Body Disease
Parkinson's Disease
Lewy Body Dementia
Parkinson's disease dementia (PDD)
Dementia with Lewy bodies (DLB)

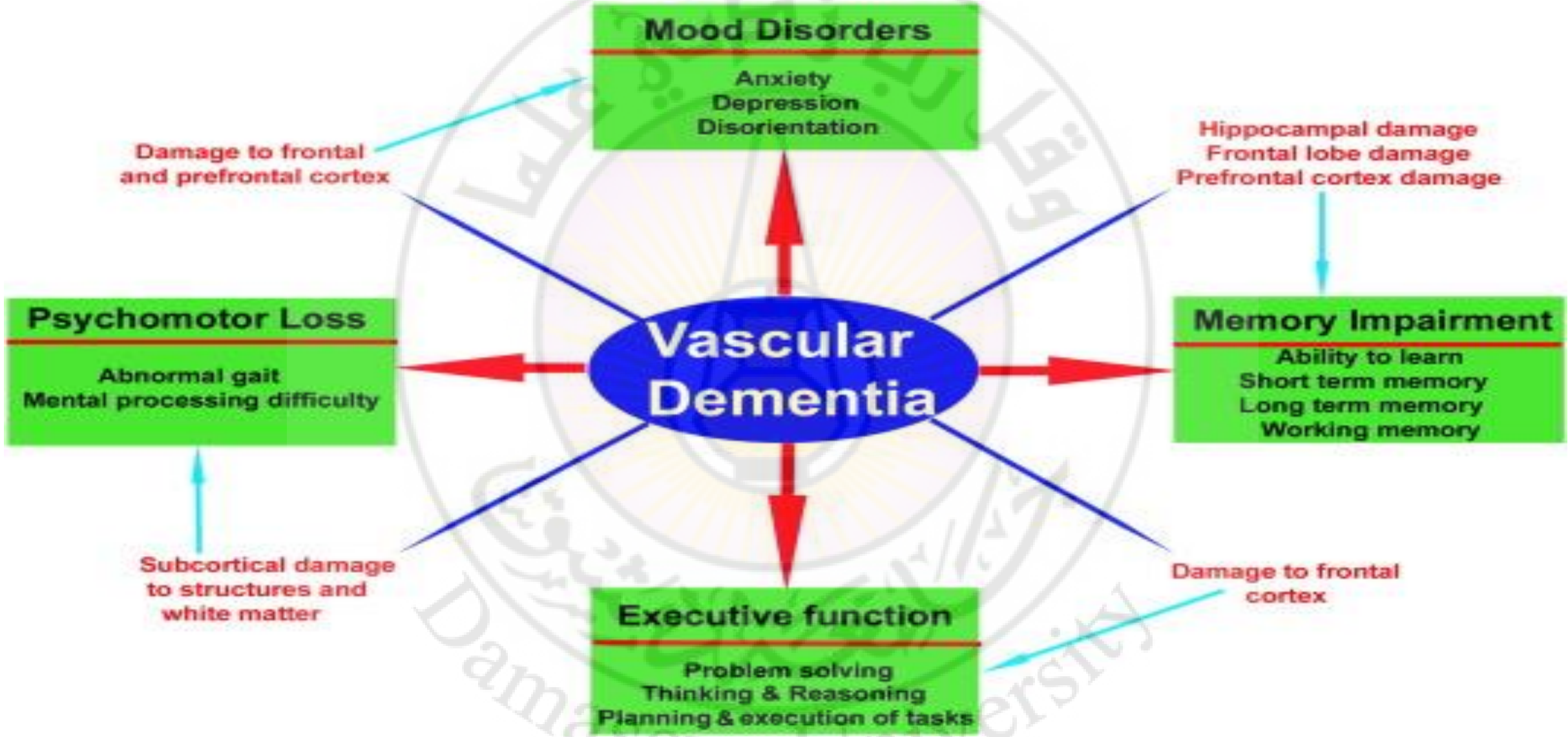


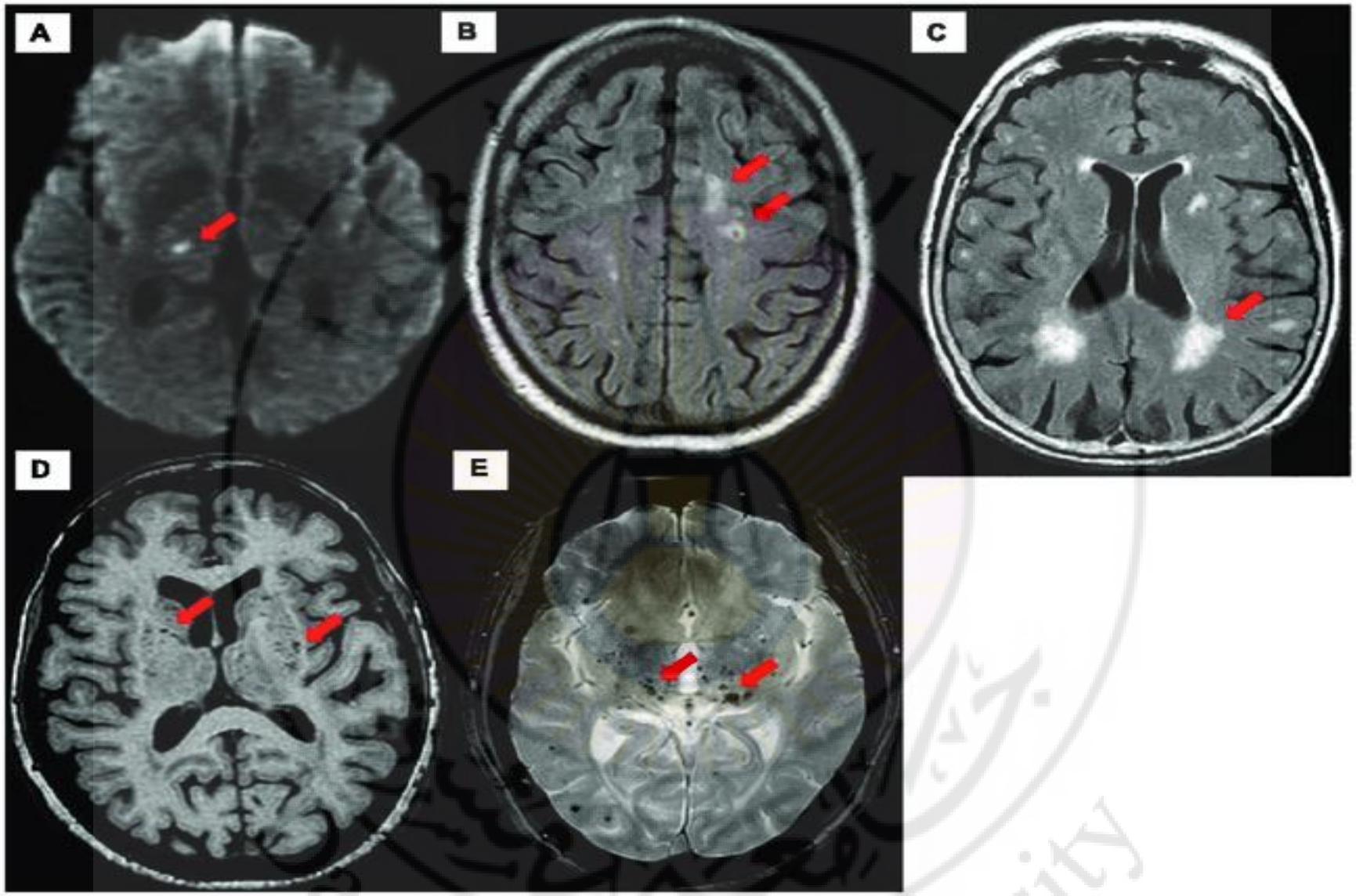
الخرف الوعائي



- اصابة أوعية دقيقة (داء سكري-ارتفاع توتر شرياني)
- اصابة المادة البيضاء تحت القشر
- اصابة المحاكمة والتقدير أولا
- اصابة الذاكرة واللغة ثانيا
- اضطراب المشي
- عدم ثبات انفعالي

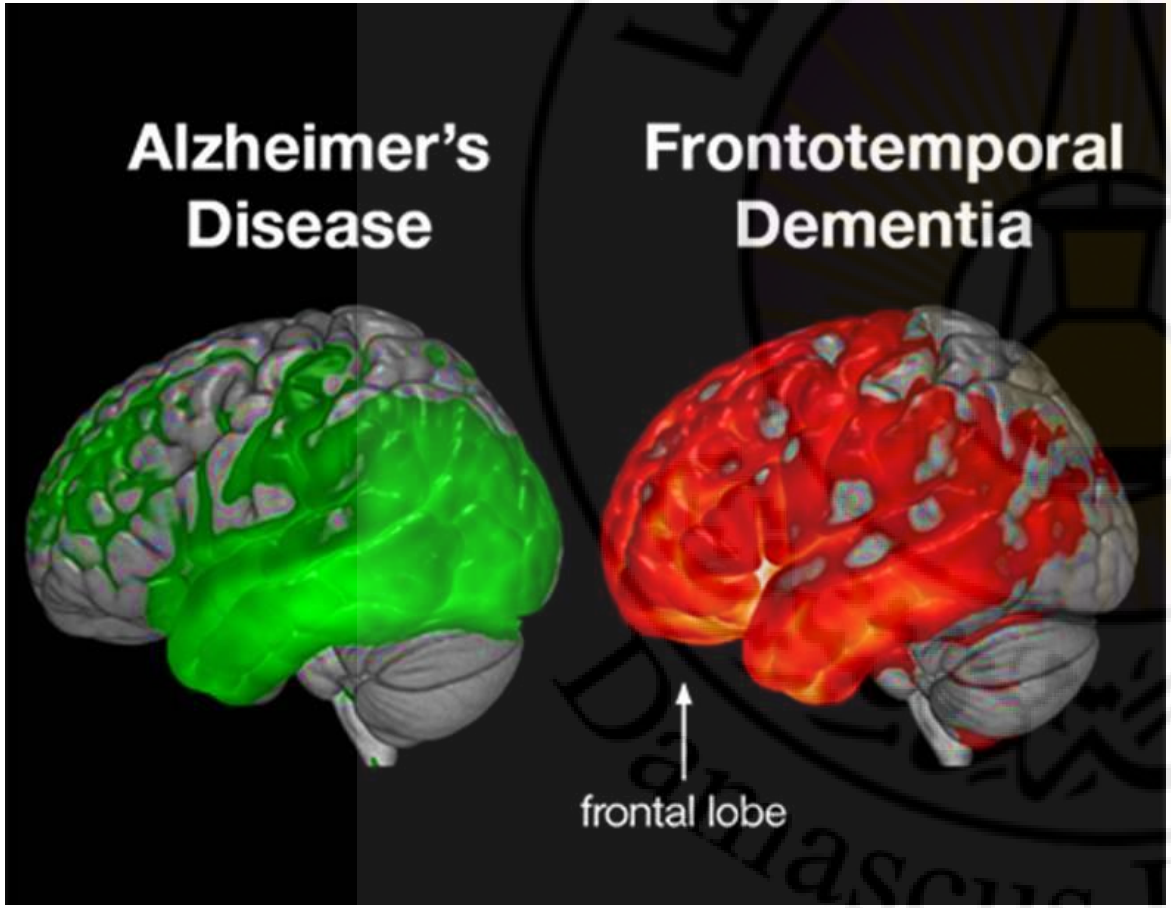

risk factors
Age
Diabetes
Hypertension
Metabolic Syndrome
any 3
Central obesity
Hypertension
Dyslipidemia
Insulin Resistance
Vascular Dementia
characteristics
Acute onset
Stepwise decline
Cardiovascular accident
Cognitive dysfunction
Neurological deficits
Neuroimaging evidence
Subtypes
stroke induced dementia
multi infarct dementia
sub cortical VaD (small vessel disease)
CADASIL
mixed dementia (VaD+AD)


Vascular Dementia
Mood Disorders
Anxiety
Depression
Disorientation
Damage to frontal and prefrontal cortex
Hippocampal damage
Frontal lobe damage
Prefrontal cortex damage
Psychomotor Loss
Abnormal gait
Mental processing difficulty
Memory Impairment
Ability to learn
Short term memory
Long term memory
Working memory
Subcortical damage to structures and white matter
Damage to frontal cortex
Executive function
Problem solving
Thinking & Reasoning
Planning & execution of tasks

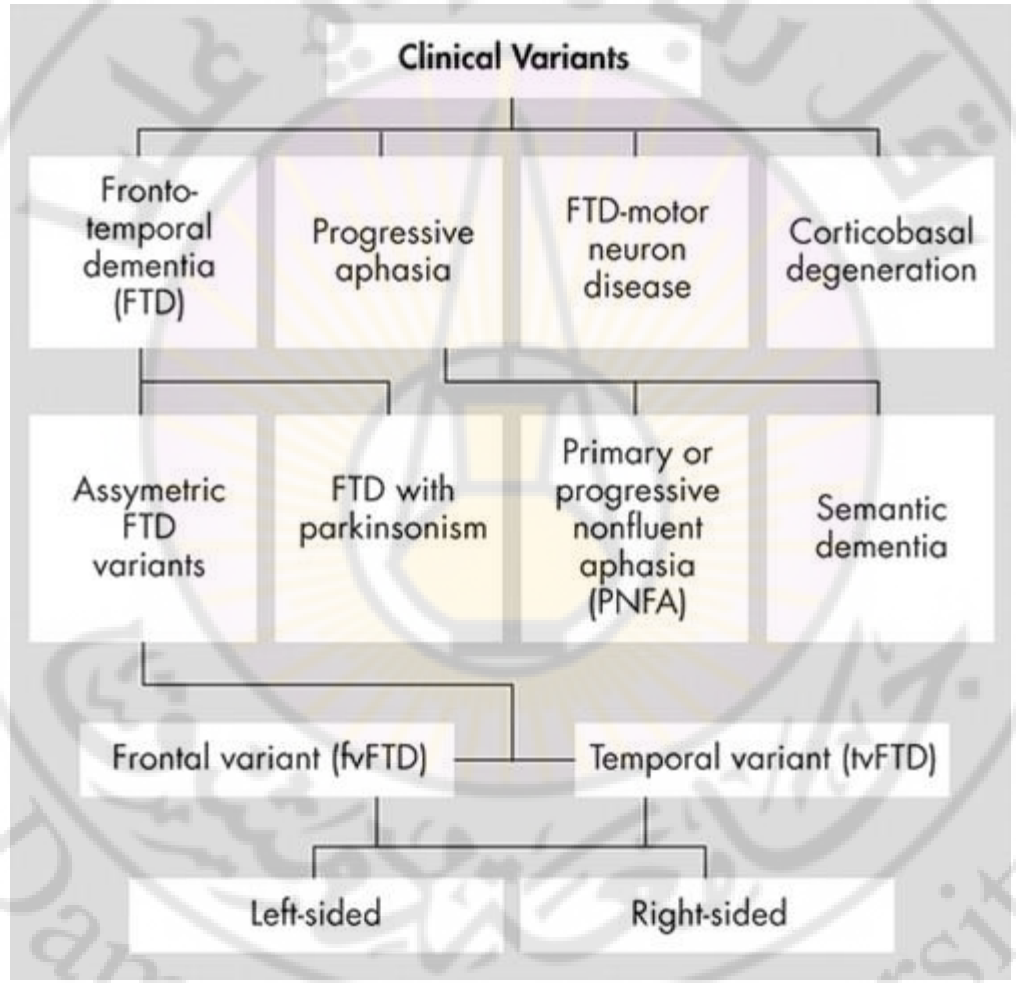


Neuroimaging classification of CSVD based on STRIVE. (A) Recent small subcortical infarct on DWI (arrow). (B) Lacune on FLAIR (arrow). (C) WMHs on FLAIR (arrow). (D) Perivascular spaces on T1-weighted imaging (arrow). (E) Cerebral microbleeds on T2 * -GRE (arrow).

Frontotemporal dementia

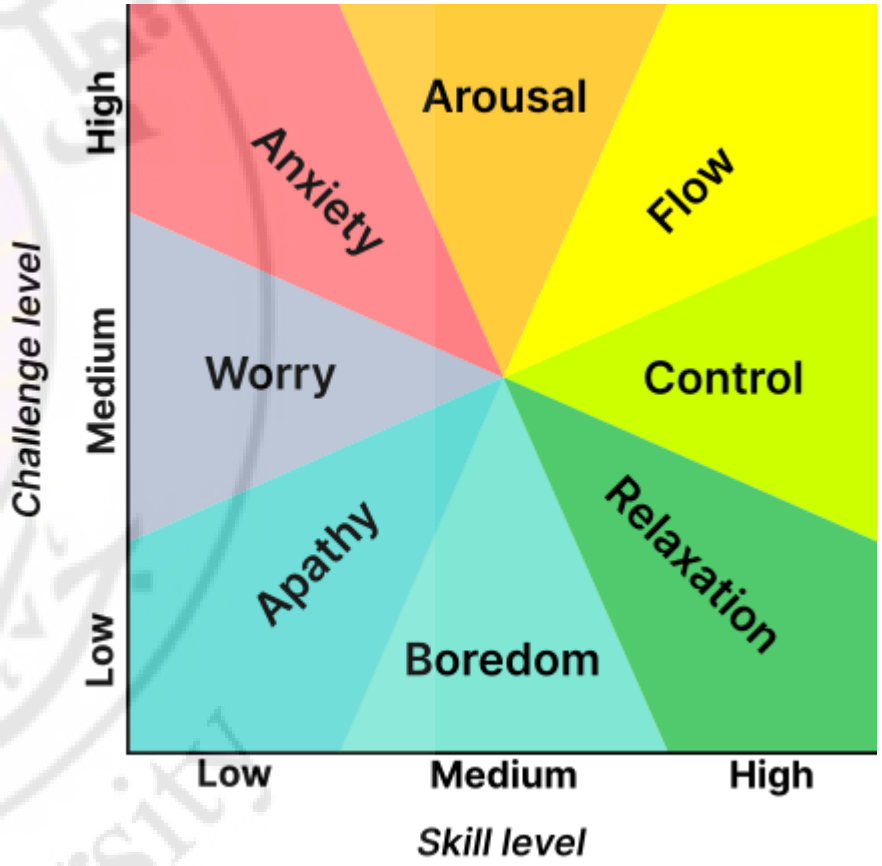


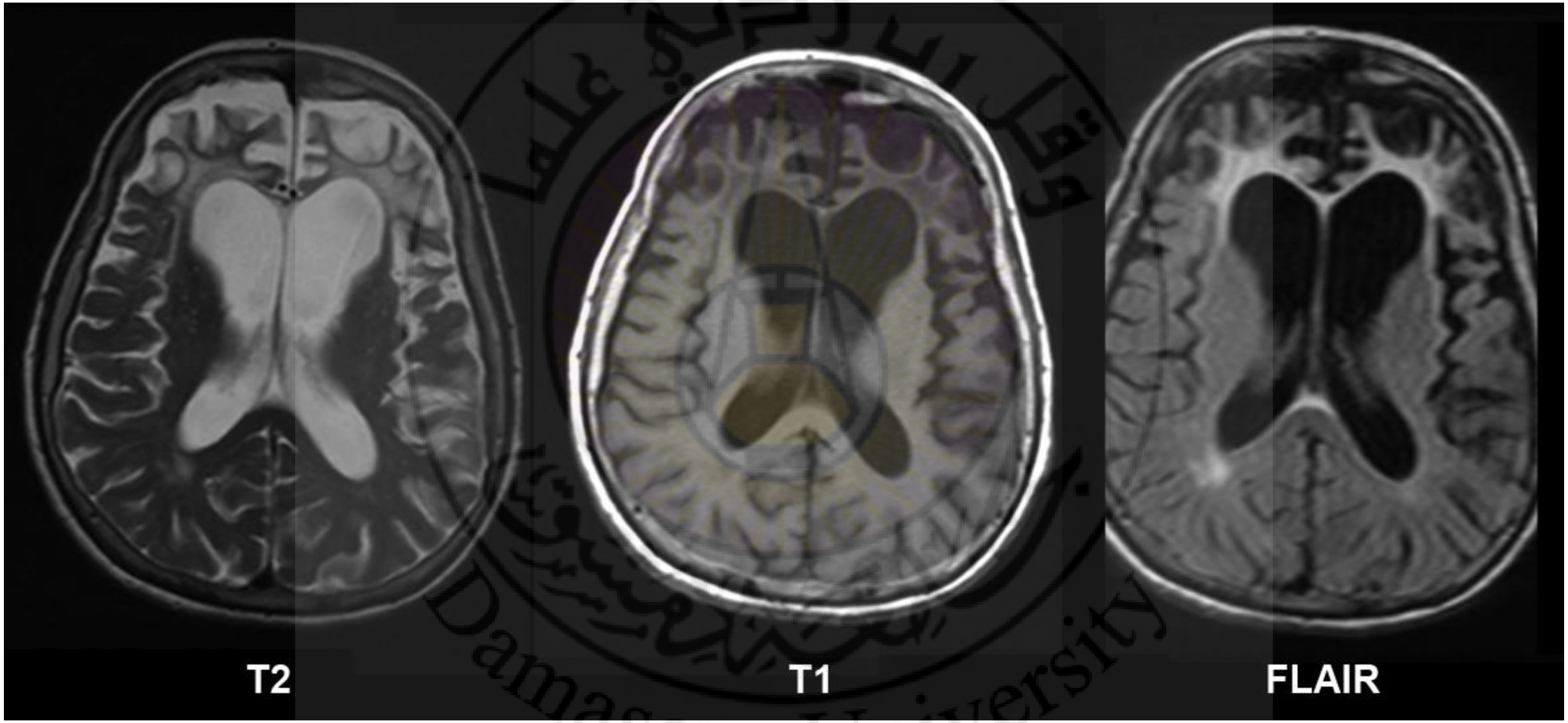
The main subtypes of frontotemporal dementia are behavioral variant FTD, semantic dementia, progressive nonfluent aphasia, and FTD associated with amyotrophic lateral sclerosis (FTD–ALS). Two distinct rare subtypes are neuronal intermediate filament inclusion disease, and basophilic inclusion body disease. Related disorders are corticobasal syndrome, and progressive supranuclear palsy


Clinical Variants
Fronto-temporal dementia (FTD)
Progressive aphasia
FTD-motor neuron disease
Corticobasal degeneration
Assymetric FTD variants
FTD with parkinsonism
Primary or progressive nonfluent aphasia (PNFA)
Semantic dementia
Frontal variant (fvFTD)
Temporal variant (tvFTD)
Left-sided
Right-sided

Six distinct clinical features have been identified as symptoms of bvFTD

1.Disinhibition
2.Apathy/Inertia
3.Loss of Sympathy/Empathy
4.Perseverative/compulsive behaviors
5.Hyperorality
6.Dysexecutive neuropsychological profile

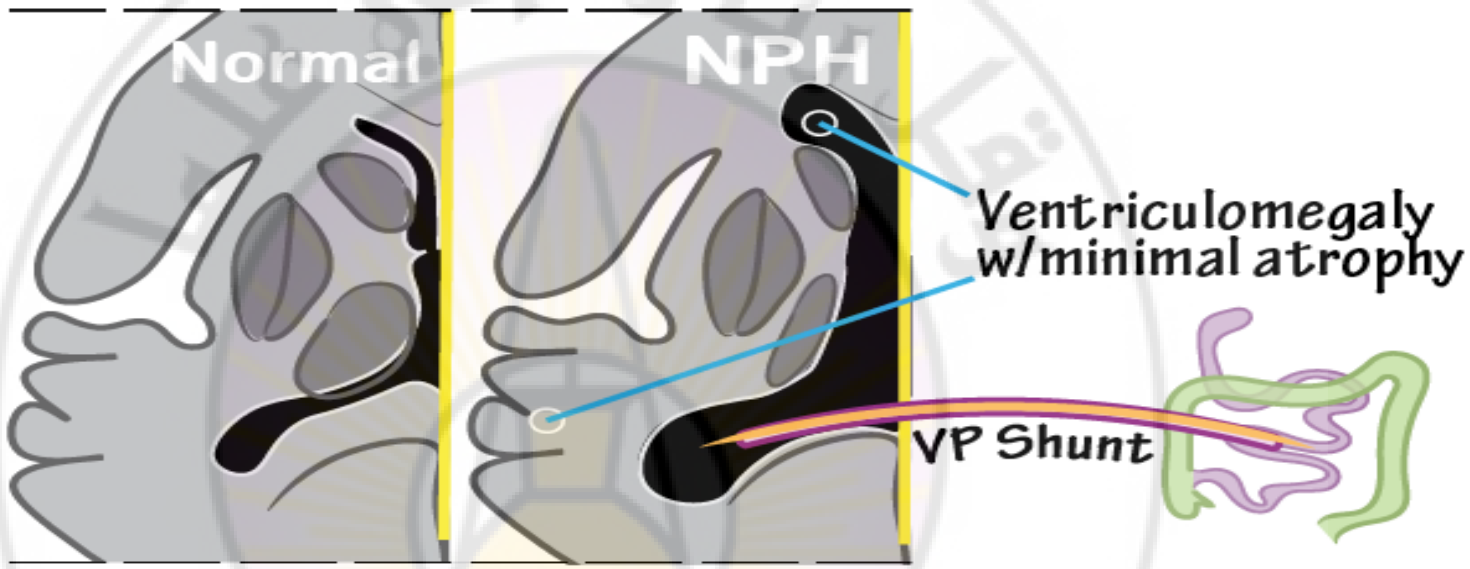



T2
T1
FLAIR

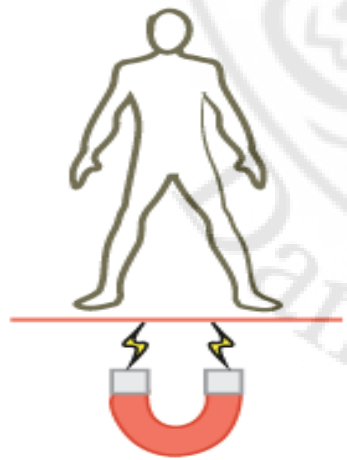
Normal pressure hydrocephalus (NPH)

Wacky

Dementia

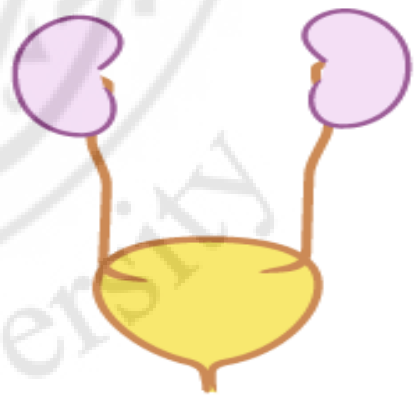


Wobbly



Magnetic gait

Wet

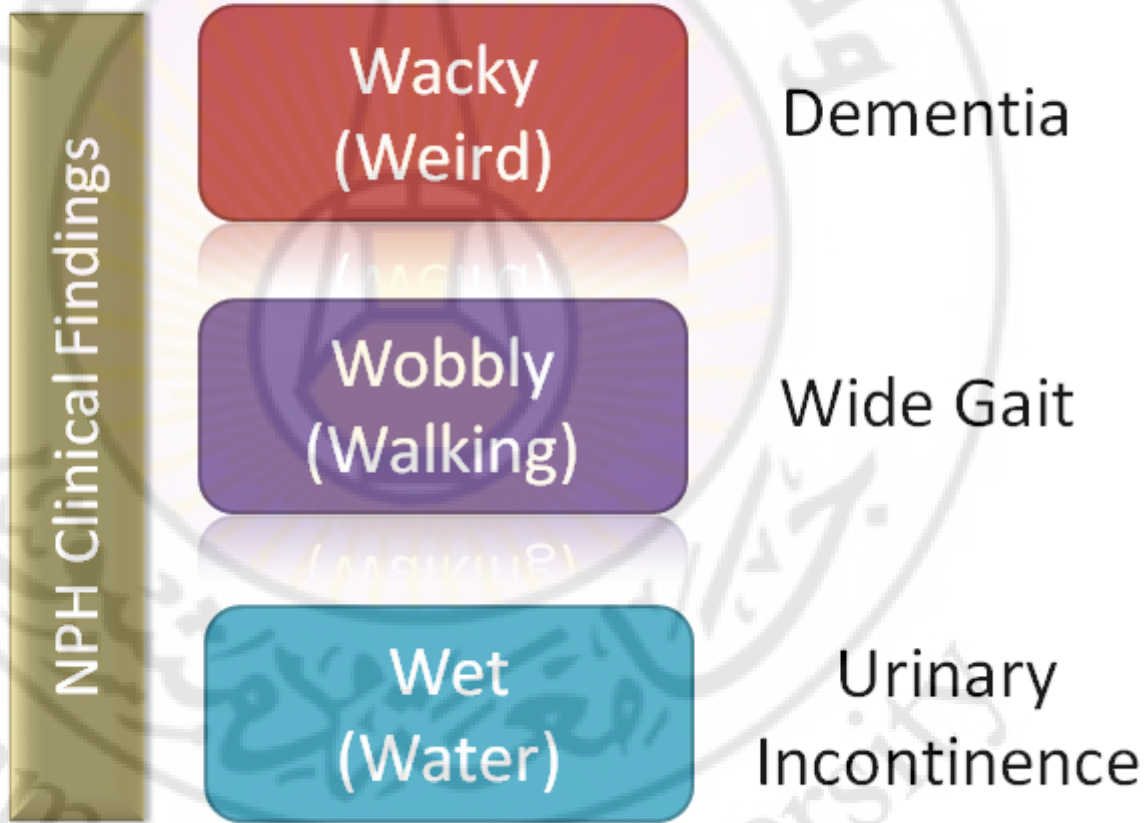


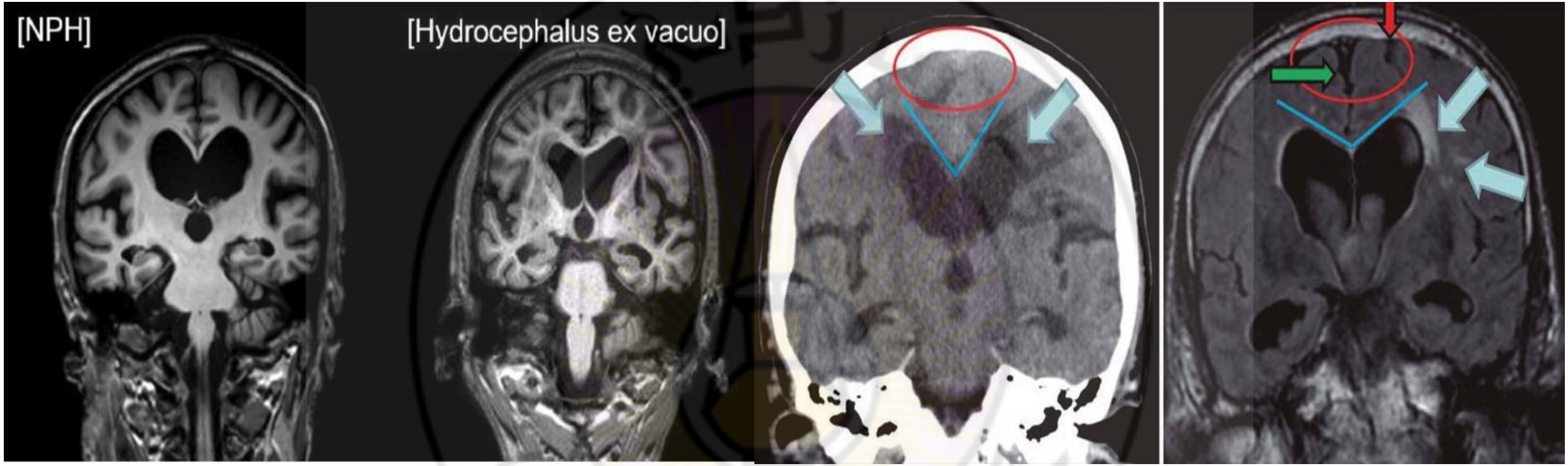
Bladder incontinence

Normal Pressure Hydrocephalus

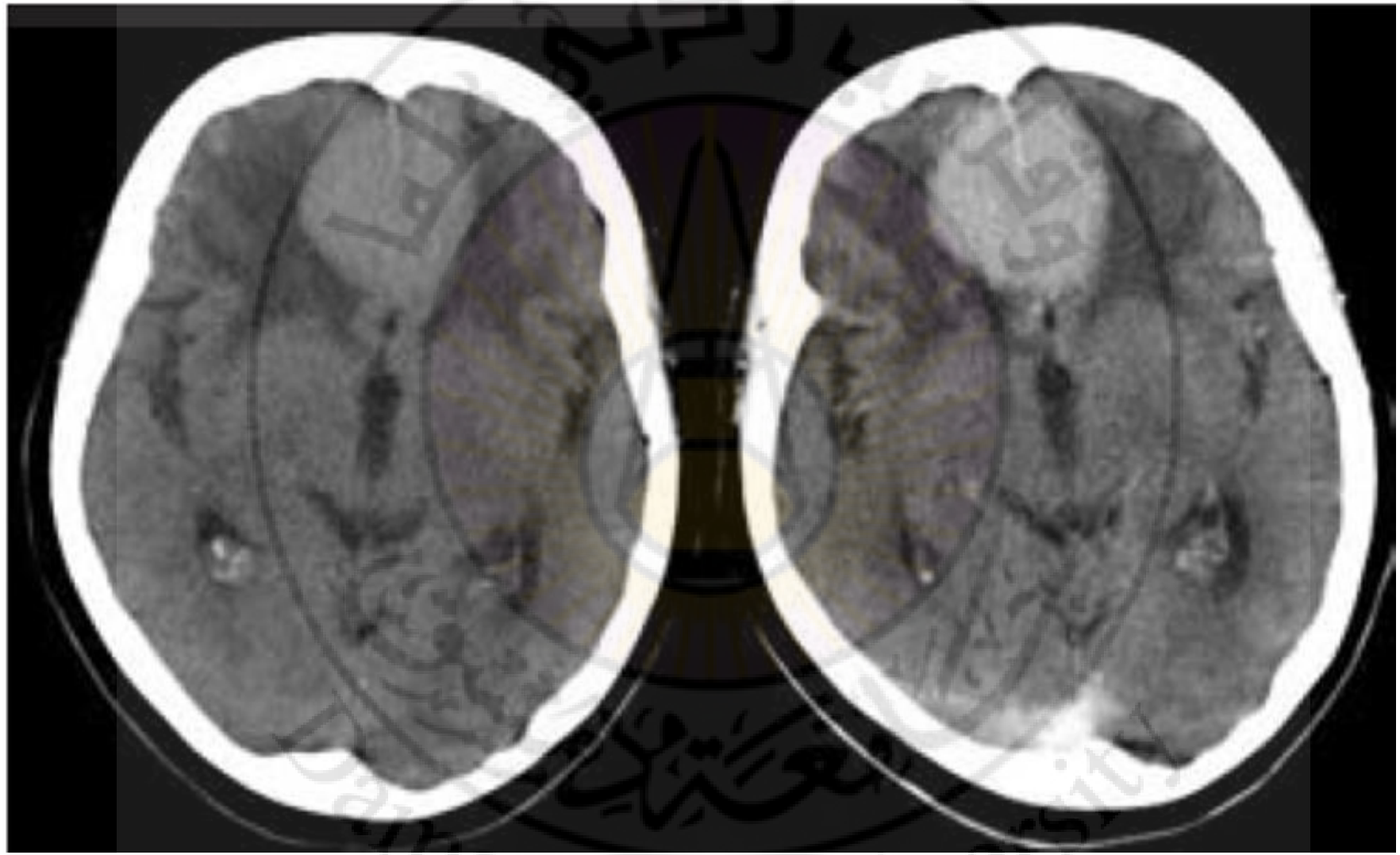
knowmedge

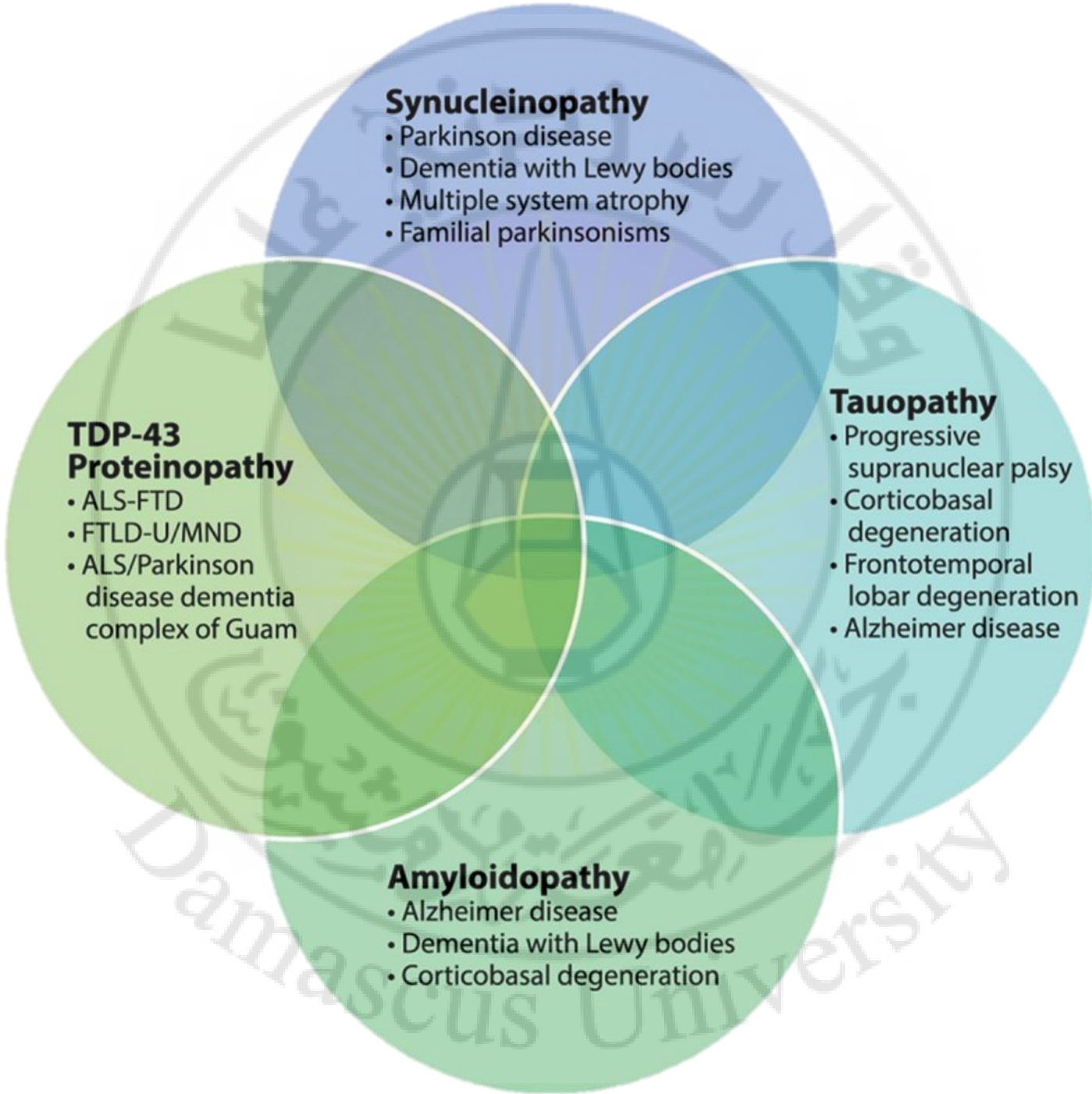
Mnemonic: "Wacky Wobbly Wet"





MRI images of the idiopathic normal pressure hydrocephalus and hydrocephalus ex vacuo. The image on the left represents iNPH, showing a small callosal angle (CA), dilatation of the Sylvian fissure, and narrowing of superior parietal sulci. The image on the right represents hydrocephalus ex vacuo with a large CA, no dilatation of the Sylvian fissure, and absence of narrowing of superior parietal sulci. iNPH: idiopathic normal pressure hydrocephalus.




Synucleinopathy
• Parkinson disease
• Dementia with Lewy bodies
• Multiple system atrophy
• Familial parkinsonisms
TDP-43 Proteinopathy
• ALS-FTD
• FTLD-U/MND
• ALS/Parkinson disease dementia complex of Guam
Tauopathy
• Progressive supranuclear palsy
• Corticobasal degeneration
• Frontotemporal lobar degeneration
• Alzheimer disease
Amyloidopathy
• Alzheimer disease
• Dementia with Lewy bodies
• Corticobasal degeneration

Cholinesterase inhibitors: two classes exist for the treatment of Dementia

Class	Inhibit
Dual ChE inhibitors	
– Rivastigmine	Both AChE
– Tacrine	and BuChE
Single ChE inhibitors	
– Donepezil	AChE

FDA-approved drugs

Drug	Target dose	Approved for	year
Tacrine	40 mg/day	Mild to moderate	1993
Donepezil	10 mg daily	All stages	1996
Rivastigmine	6 mg twice daily or 9.5-mg patch daily	All stages	2000
Galantamine	target dose 24	Mild to	2001

Disease-Modifying Agents

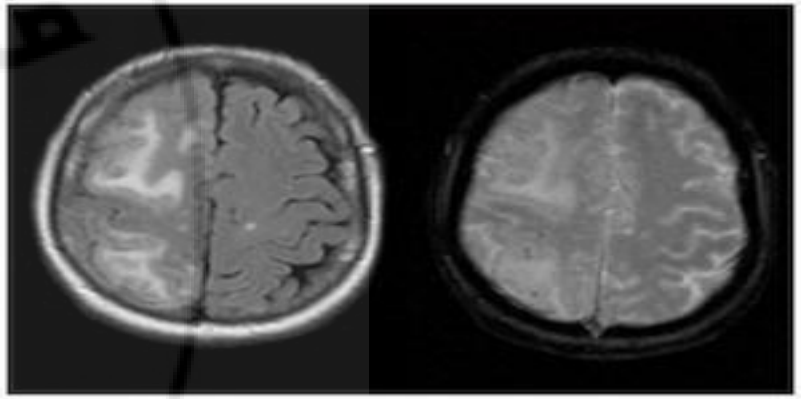
Proposed or unregulated drugs which require further studies

- Selegeline
- Vit-E
- Oestrogen
- Prednisolone
- NSAIDs
- Ginkgo biloba
- Glycogen syntehtase kinase 3 (GSK 3)
- β-secretase inhibitors
- γ-secretase inhibitors

Active and passive beta amyloid immunisation against AD

- ***Vaccination against $A\beta_{42}$*** has proved highly efficacious in mouse models of AD, helping clear brain amyloid and preventing further amyloid accumulation.
- In human trials, this approach led to ***life-threatening complications***, including ***meningoencephalitis***

It is an amyloid beta-directed monoclonal antibody



Amyloid-related imaging abnormalities (ARIA) are monitored by magnetic resonance imaging of the brain one to two times per year

After an initial titration period, Aduhelm is to be administered at a maintenance dose of 10 mg/kg, given as an intravenous infusion over about one hour every four weeks.


مين هاد
أمي حبيبتي

بسم الله الرحمن الرحيم

Motor neuron disease, peripheral neuropathy and muscle disease

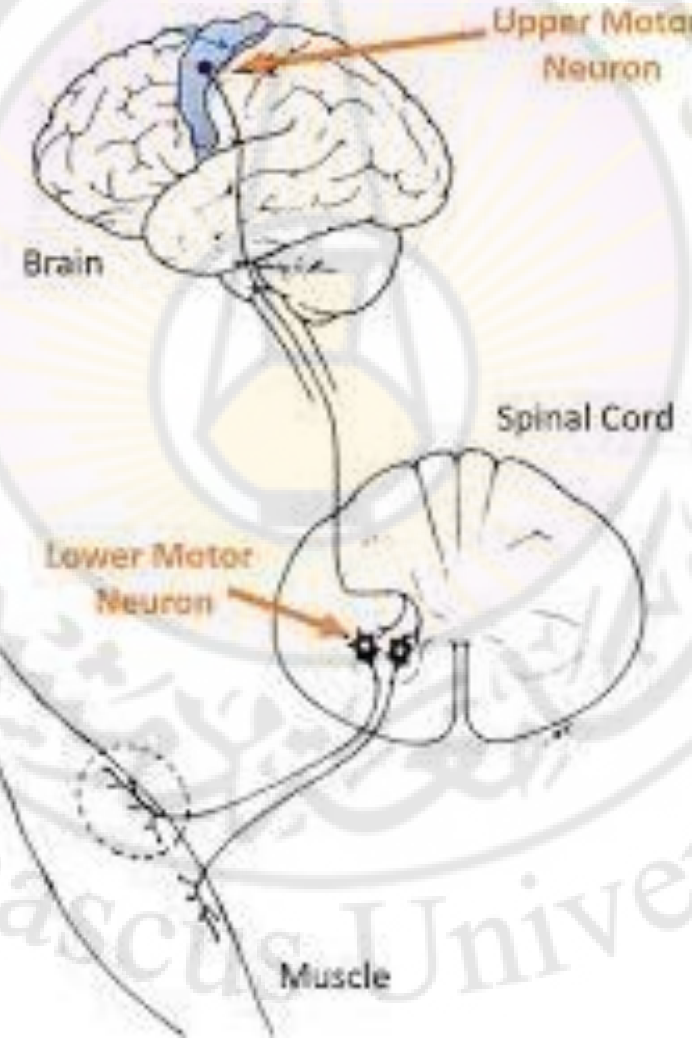
Prof. Mohamad Shehadeh Agha

MD MRCP (London) FRCP (Edin)

Motor neuron disease

The process is remarkably selective, leaving special senses, and cerebellar, sensory and autonomic functions intact

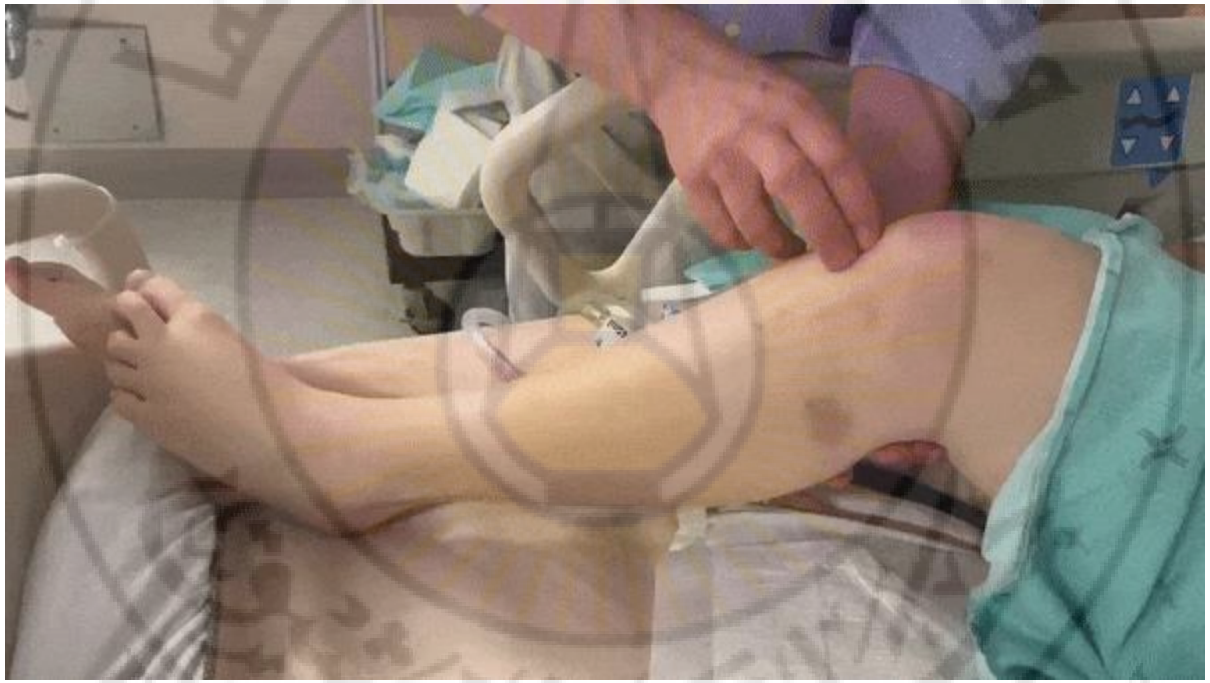
No
Sense
Eye
Autonomic
Cerebellar
Cognition
Bed sores



Motor neuron disease

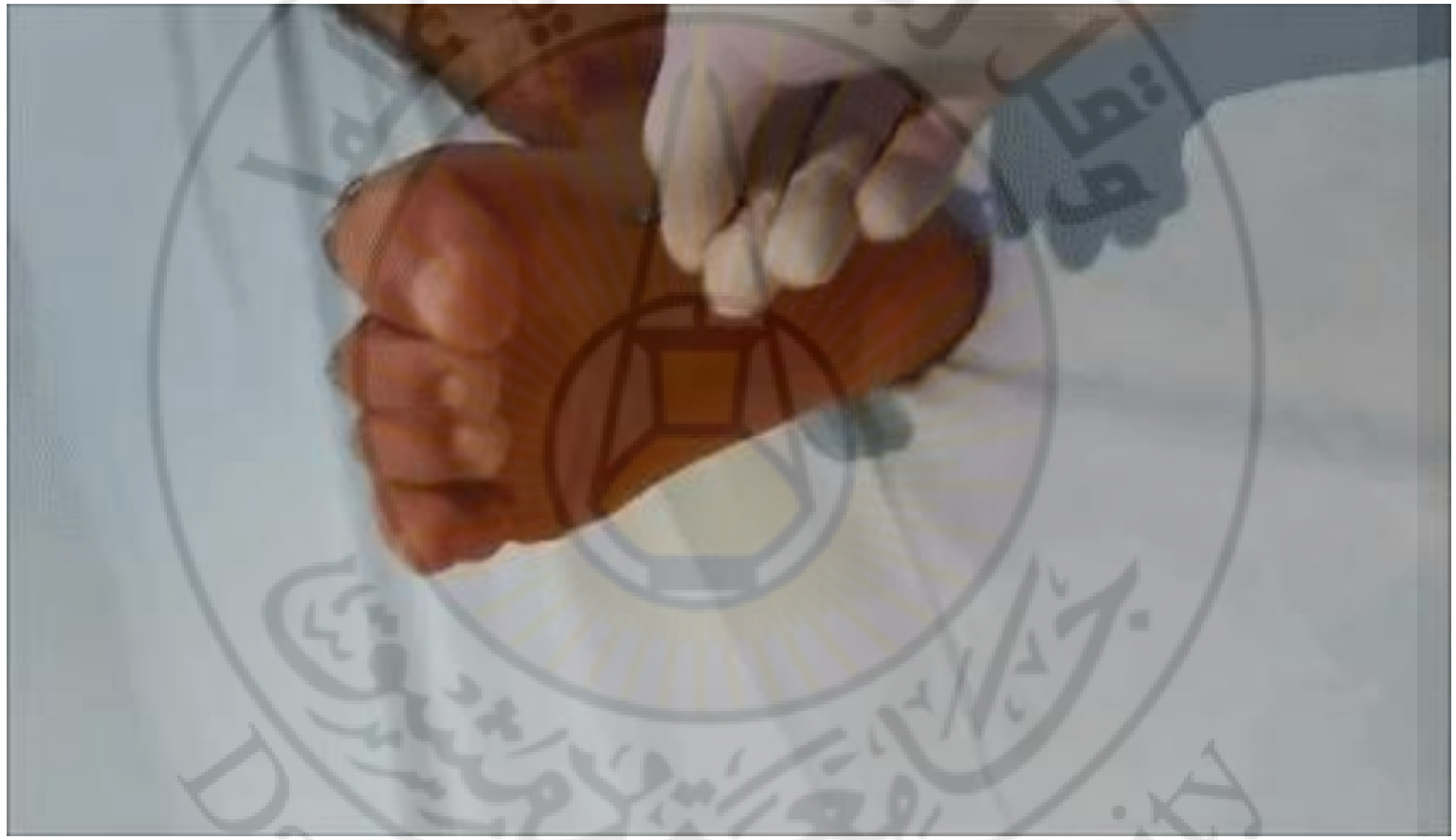
Key features of motor neurone disease

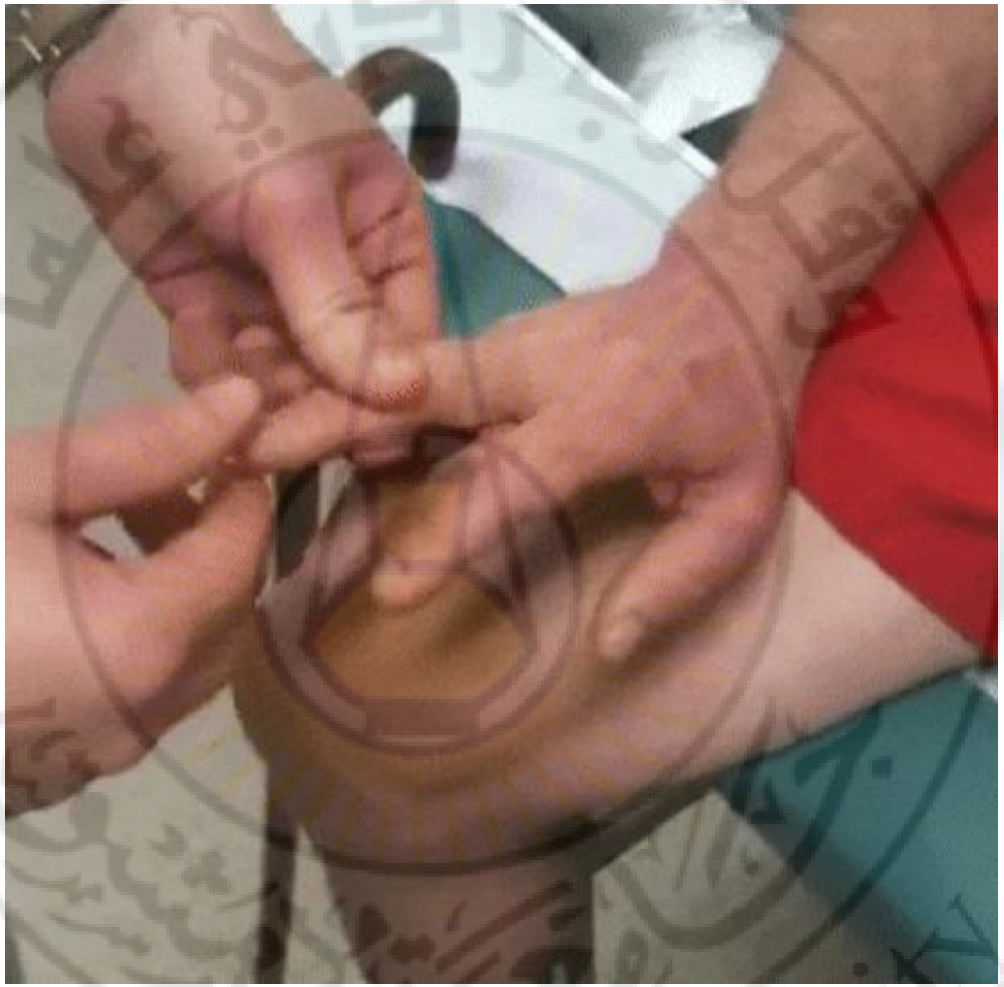
- Muscle weakness
- Muscle wasting
- Muscle fasciculation
- Exaggerated reflexes
- No loss of sensation



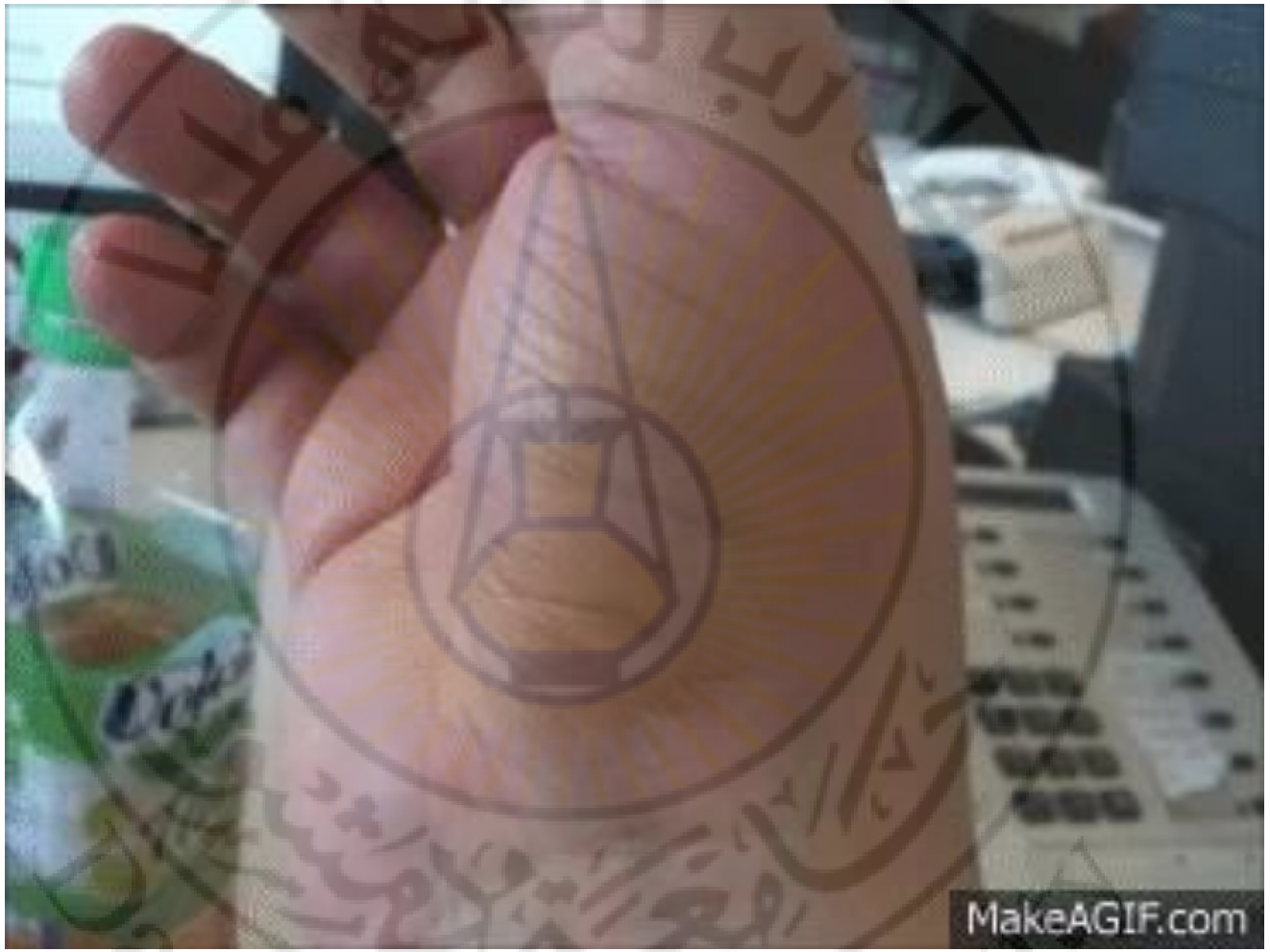
Hyperreflexia

Clonus

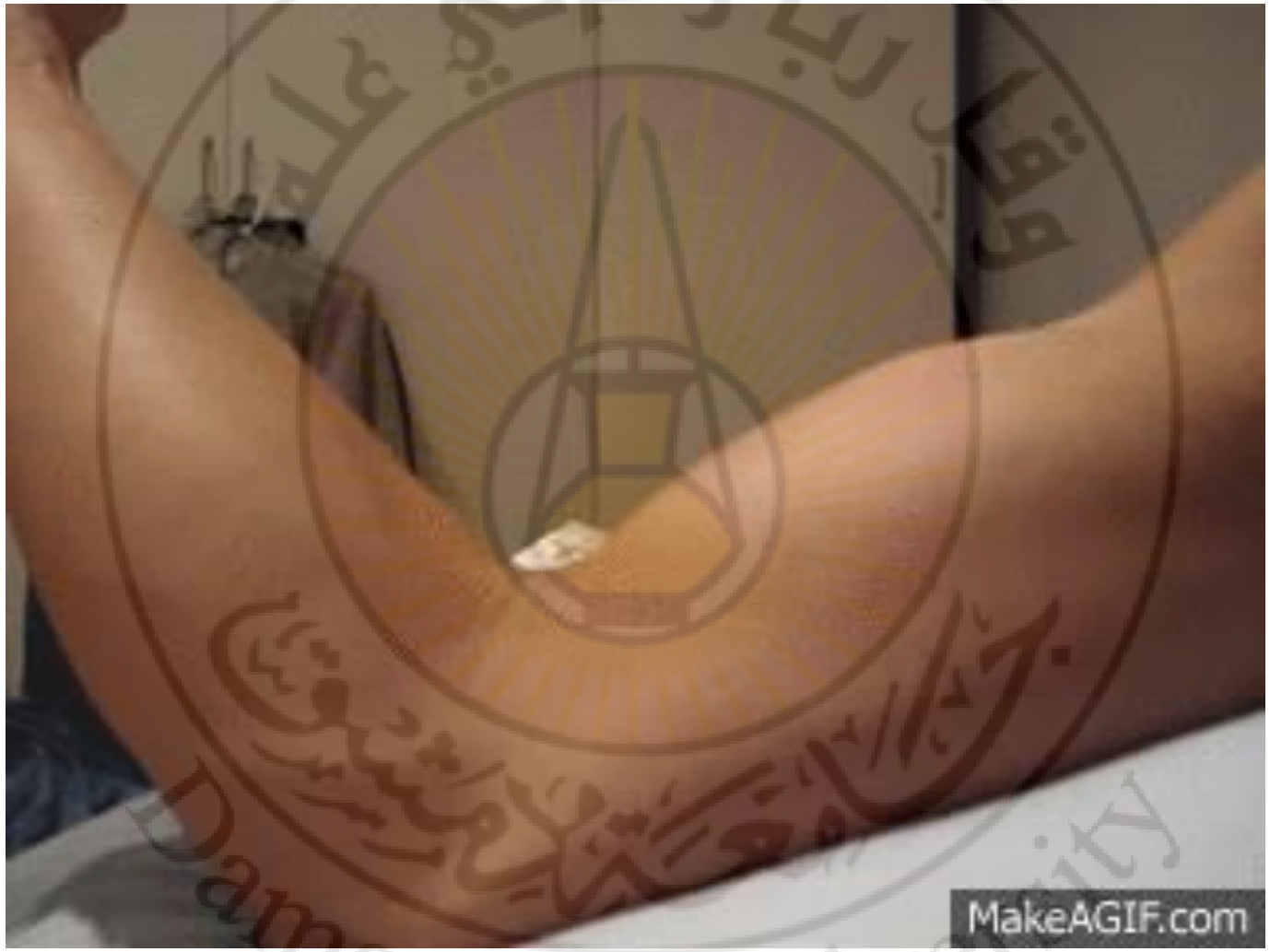




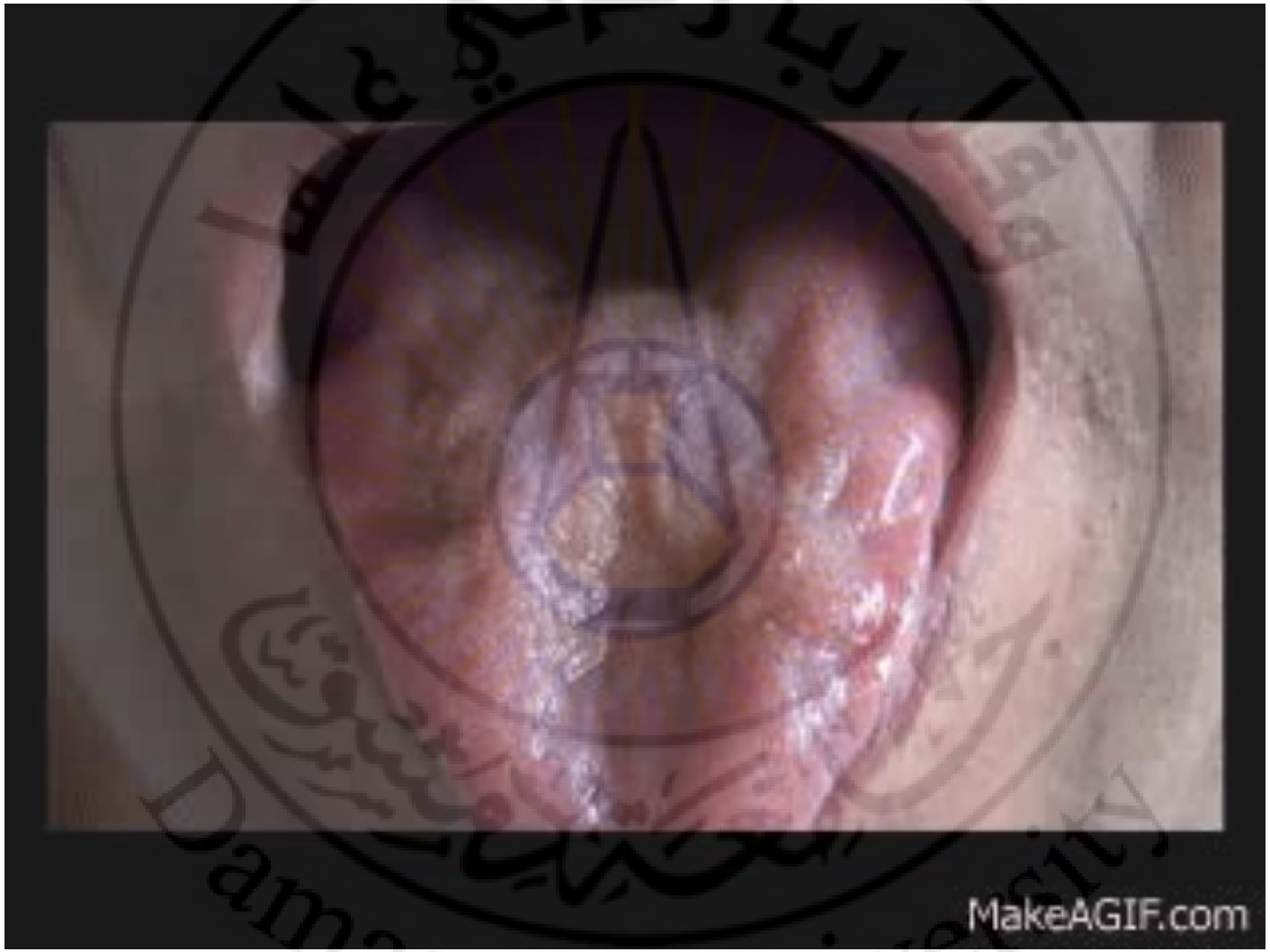
Hoffman’s sign



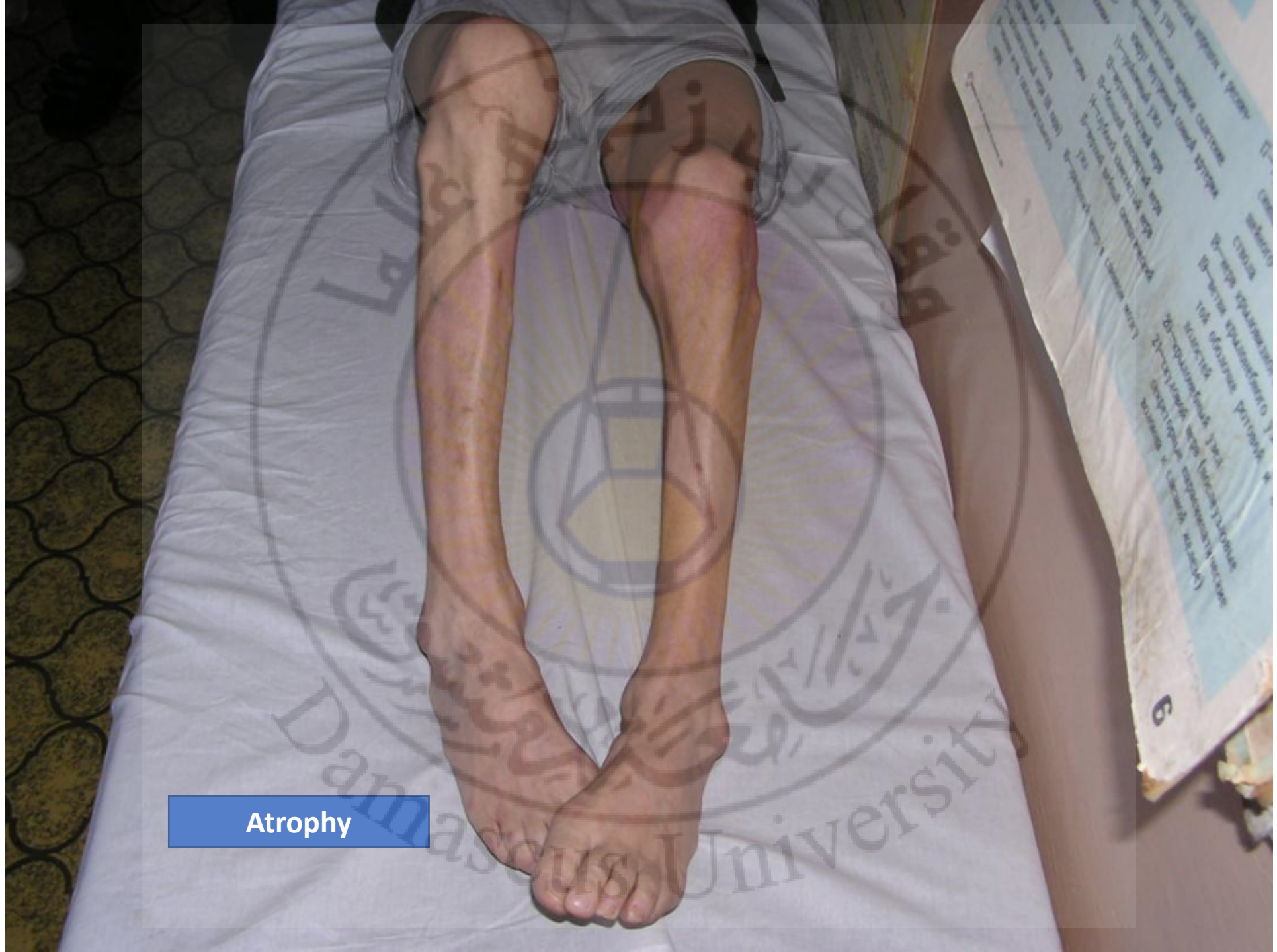
Fasciculation

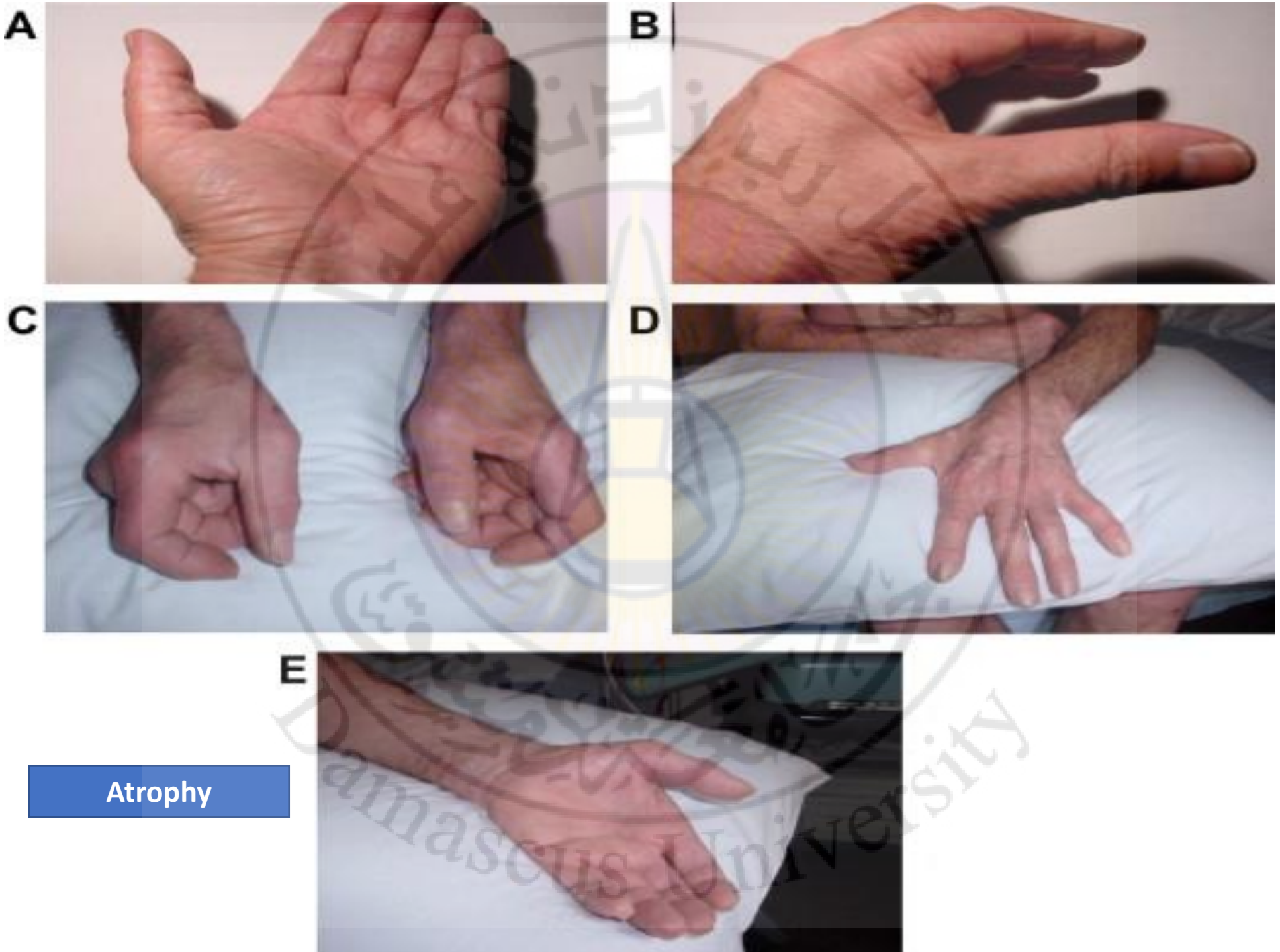


Fasciculation

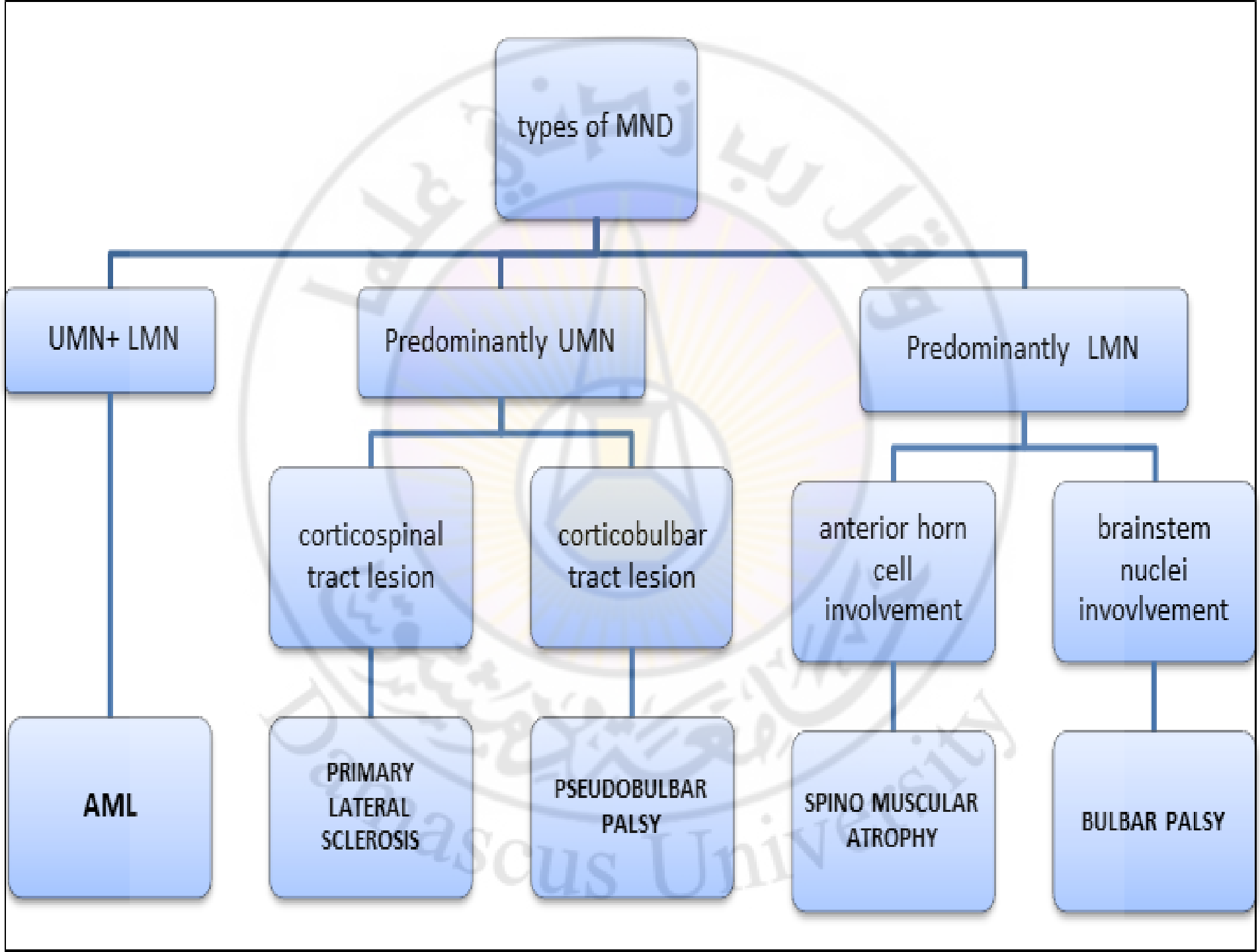


Fasciculation

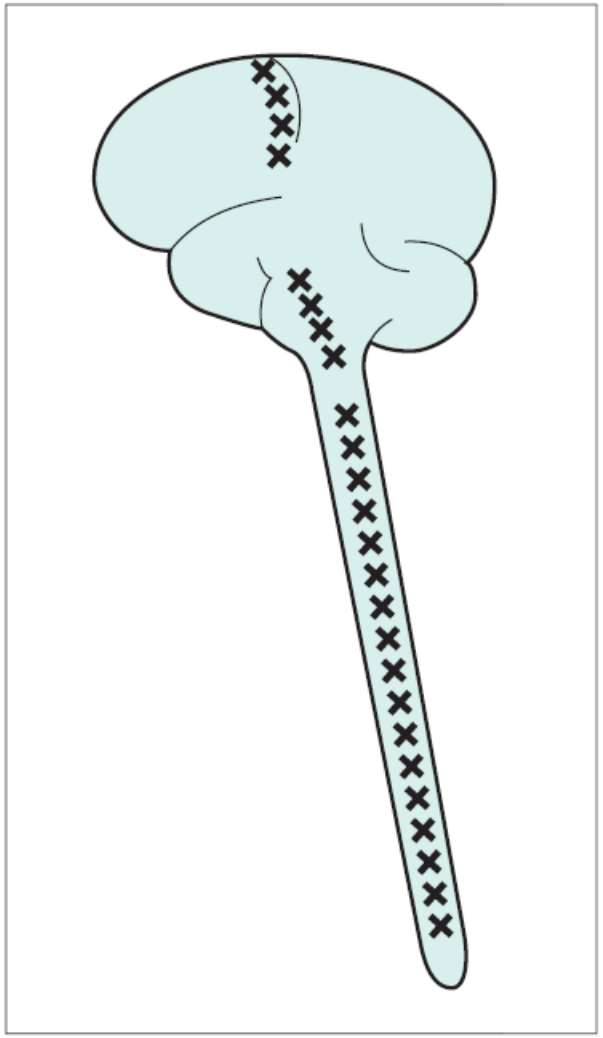

Atrophy



Atrophy


types of MND
UMN+ LMN
Predominantly UMN
Predominantly LMN
corticospinal tract lesion
corticobulbar tract lesion
anterior horn cell involvement
brainstem nuclei invovlvement
AML
PRIMARY LATERAL SCLEROSIS
PSEUDOBULBAR PALSY
SPINO MUSCULAR ATROPHY
BULBAR PALSY

Motor neuron disease



Lower motor neurone — **Upper motor neurone**

Muscles supplied by the lower cranial nerves

Bulbar palsy

Weakness, wasting and fasciculation of the lower facial muscles, and muscles moving the palate, pharynx, larynx and tongue—most conspicuous in the tongue

Pseudobulbar palsy

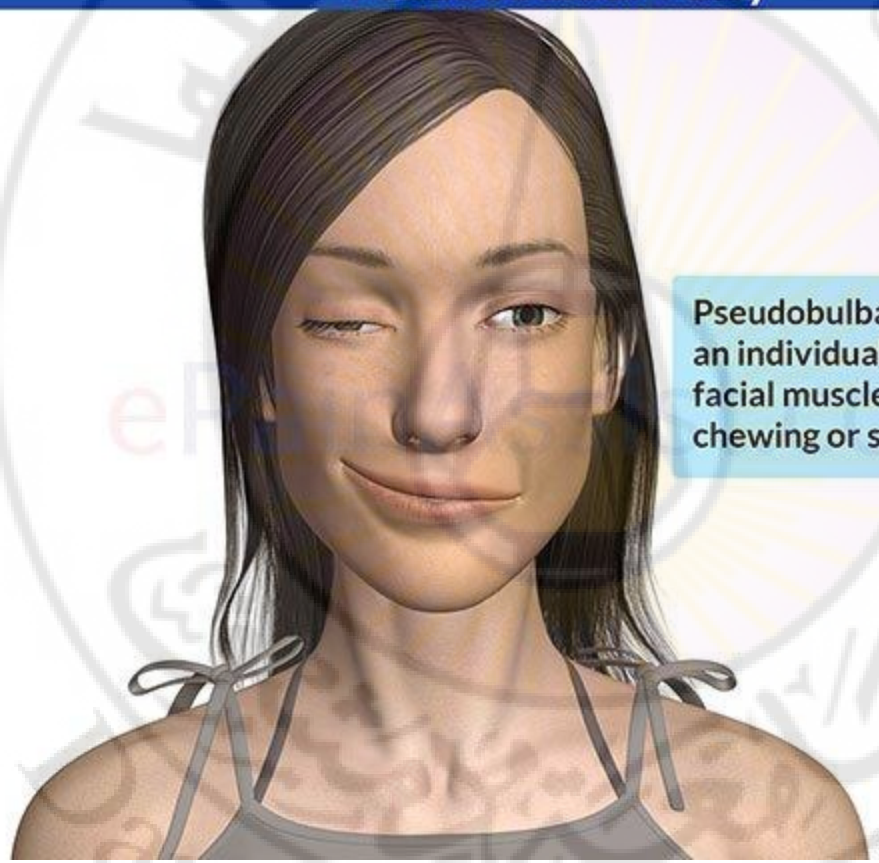
Weakness, slowness and spasticity of the lower facial muscles, jaw, palate, pharynx, larynx and tongue muscles

Exaggerated jaw-jerk

Emotional lability

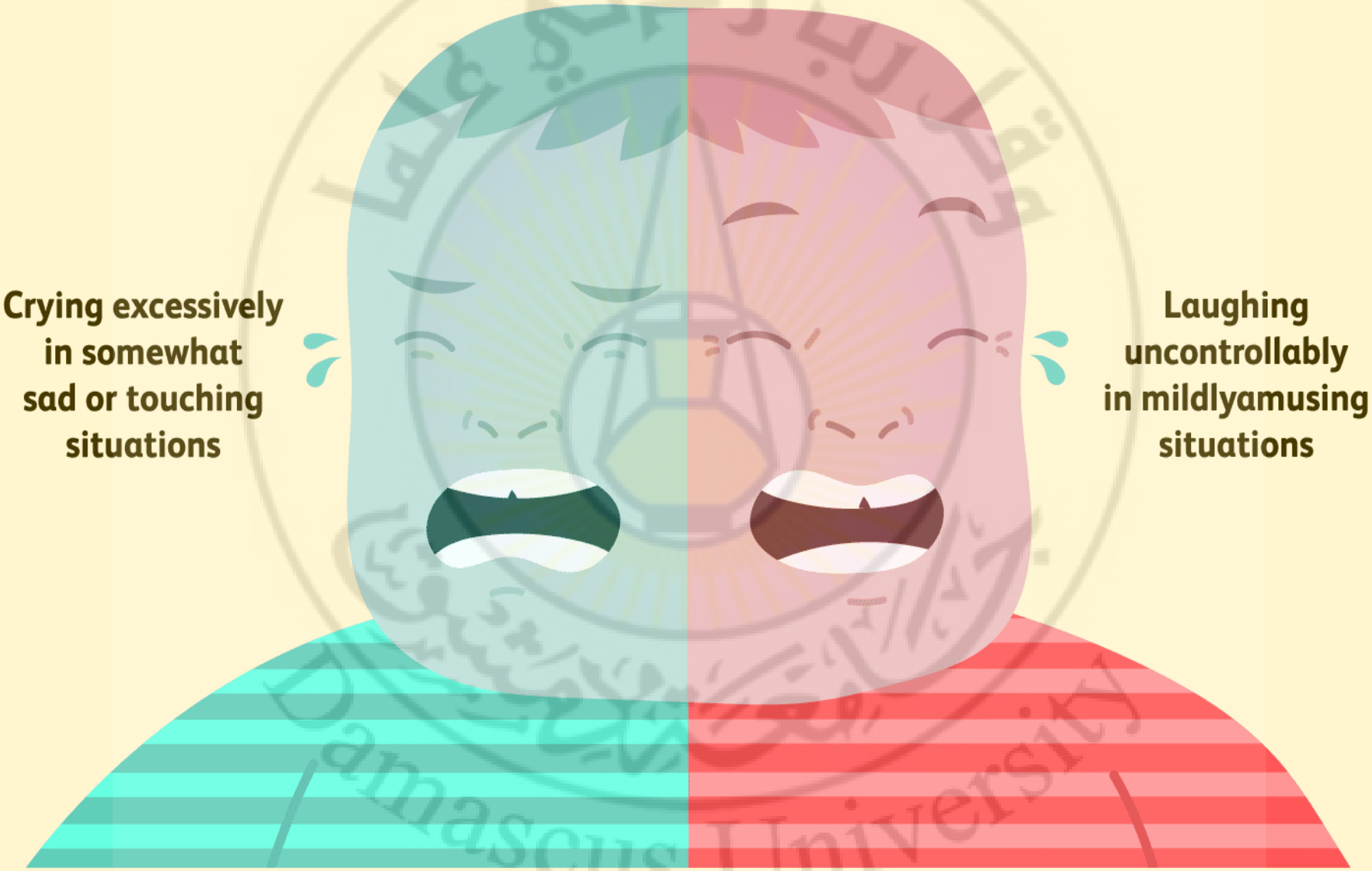
Dysarthria, dysphagia, weight loss and the risk of inhalation pneumonia are the clinical problems facing patients described above

Pseudobulbar Palsy



Pseudobulbar Palsy in which an individual loses control of facial muscles and has trouble chewing or speaking etc.

Symptoms of Pseudobulbar Affect

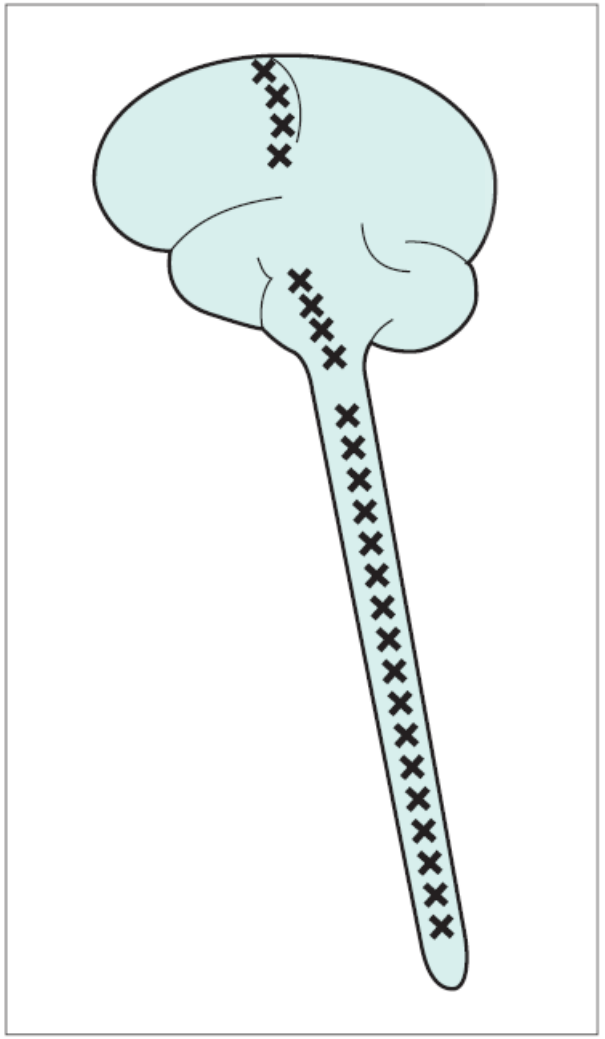


Crying excessively in somewhat sad or touching situations

Laughing uncontrollably in mildlyamusing situations

Crying or laughter that persists for a considerable period of time

Motor neuron disease



Muscles of the limbs and trunk

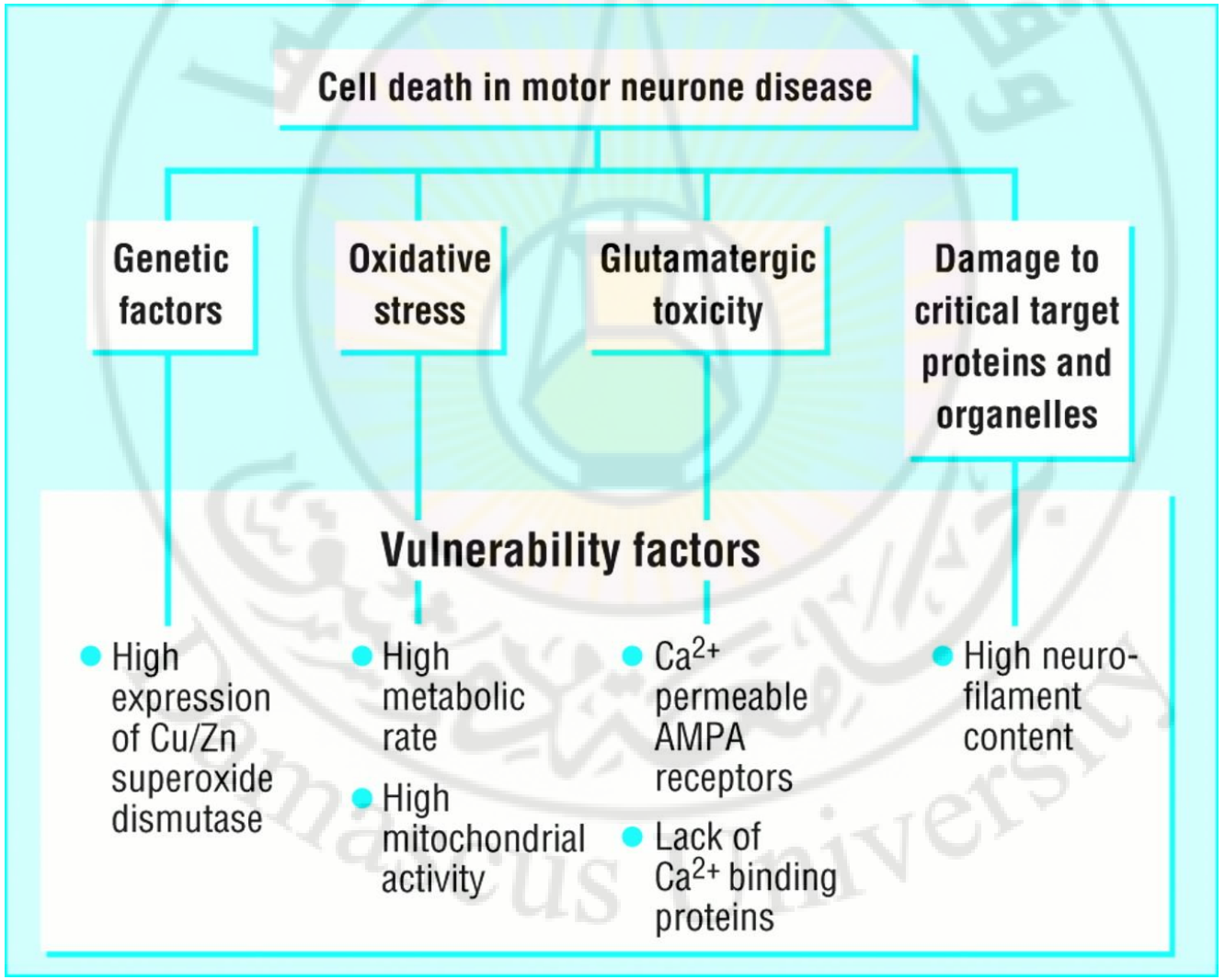
Progressive muscular atrophy

- Weakness, wasting and fasciculation of any of the limb or trunk muscles
- Often associated with frequent muscle cramps
- No sensory loss
- Small muscles of the hand frequently involved

Amyotrophic lateral sclerosis

- Weakness, spasticity, clonus and increased deep tendon reflexes
- Any limb, but more commonly in the legs
- Sphincter control not affected
- No sensory loss

Motor neuron disease



Motor neuron disease

PHARMACOLOGIC TREATMENT

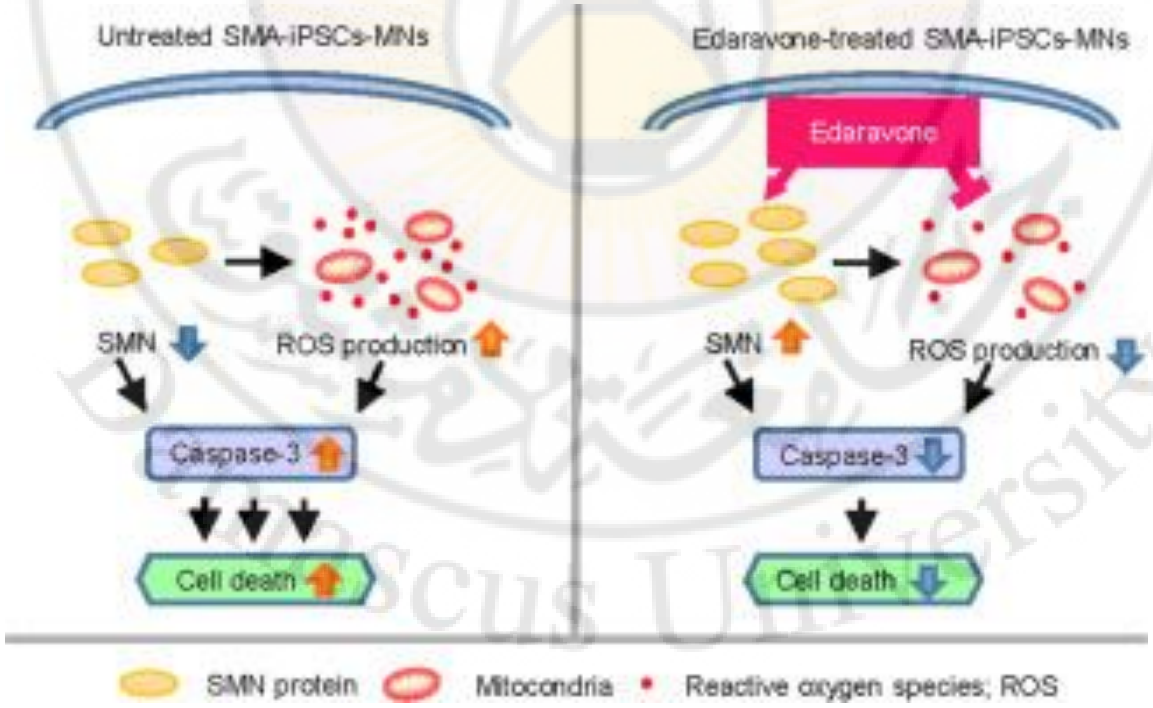
Motor neuron disease

2022

Relyvrio is an oral medication approved to treat adults with ALS. It's a combination of two different active ingredients: Sodium phenylbutyrate: a medication currently used to lower ammonia levels in the blood. Taurursodiol: a cousin of ursodiol, a medication currently used to treat gallstones

Edaravone (Radicava)

In May 2017, I.V. edaravone was approved by the FDA to treat people with amyotrophic lateral sclerosis (ALS) in the United States.



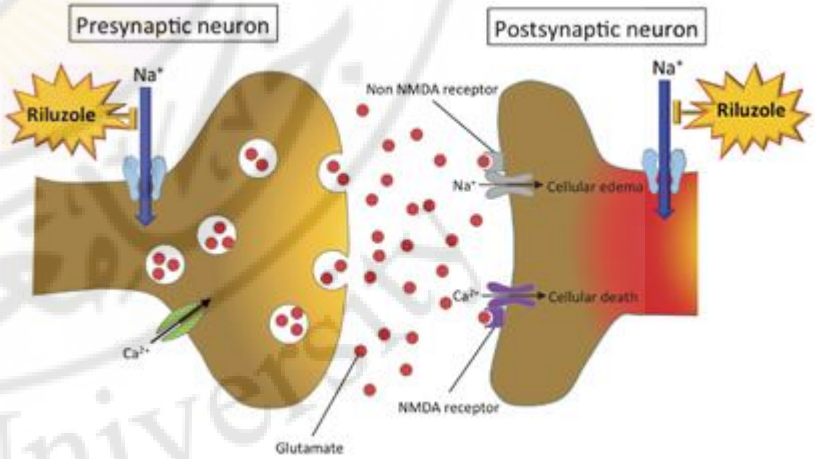
Riluzole

Riluzole — Three separate mechanisms of riluzole are thought to reduce glutamate-induced excitotoxicity:

1. inhibition of glutamic acid release

2. noncompetitive block of NMDA receptor mediated responses

3. direct action on the voltage-dependent sodium channel



Dose and side effects — The recommended dose of Riluzole is 100 mg per day.

Motor neuron disease

SUPPORTIVE TREATMENT

Muscle spasm & weakness

- **Baclofen 5 to 10 mg twice daily to three times daily.**
- **Tizanidine 2 to 4 mg by mouth twice daily up to a total dose of 24 mg daily.**
- **Memantine starting at 5 mg daily, increasing by 5 mg a week to a maximum of 20 mg twice a day.**
- **Tetrazepam 50 mg at bedtime, increasing by 25 mg a day to a maximum dose of 150 mg taken two to three times a d**ay.

Secretion management

- **Non-pharmacologic management**
  - **Suction machine (not usually helpful for thick mucus, but helpful with sialorrhea)**
  - **Mechanical insufflation-exsufflation (In-Exsufflator cough machine)**
  - **Manually assisted coughing techniques**

Pseudobulbar Affect

- Also known as: pseudobulbar palsy, emotional incontinence, pathologic crying/laughing
- The emotional lability is NOT a mood disorder, but is an uncontrolled outburst and is a very troubling symptom for patients.
- It is an abnormal affective display that can be seen in about 50% of ALS patients.

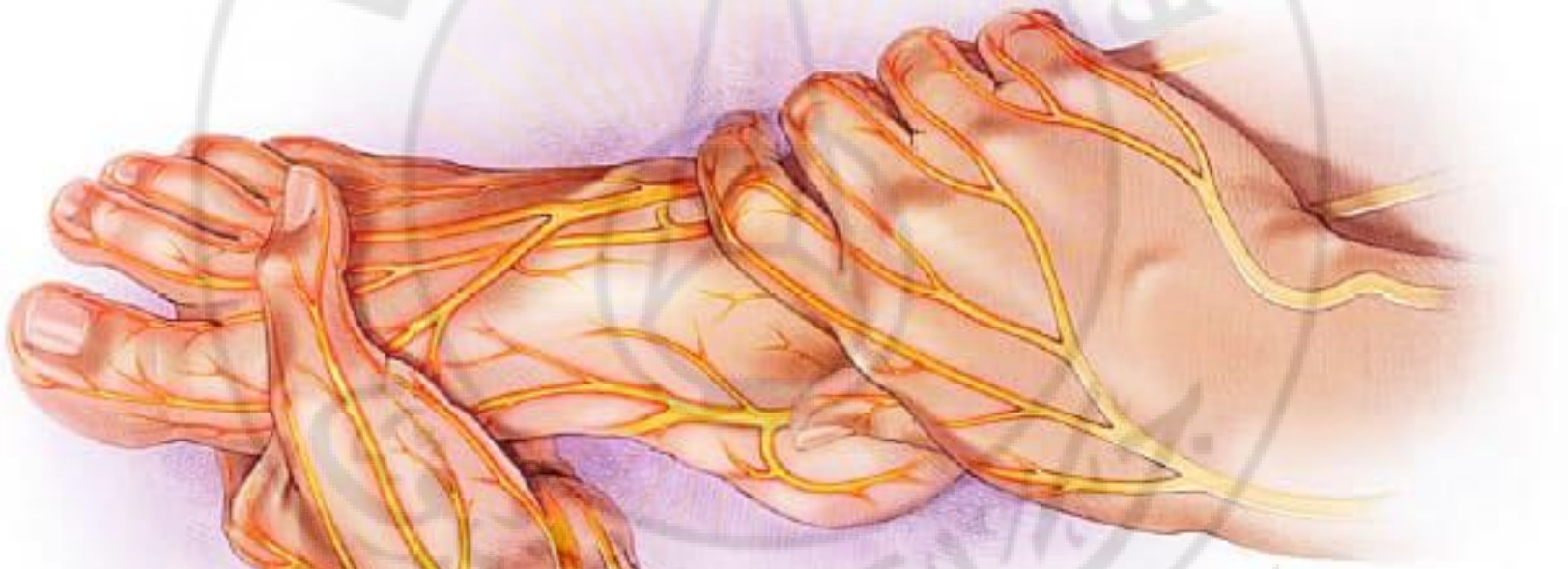
Pseudobulbar Affect

- Amitriptyline 100-150mg QHS
- Fluvoxamine 100-200mg QD
- Alternatively may try Lithium or L-Dopa
- a novel approach utilizing dextromethorphan and quinidine sulfate. Nuedexta is an FDA approved medication for pseudobulbar affect. Dextromethorphan, an N-methyl-D-aspartate receptor antagonist, inhibits glutamatergic transmission in the regions of the brainstem and cerebellum, which are hypothesized to be involved in pseudobulbar symptoms, and acts as a sigma ligand, binding to the sigma-1 receptors that mediate the emotional motor expression

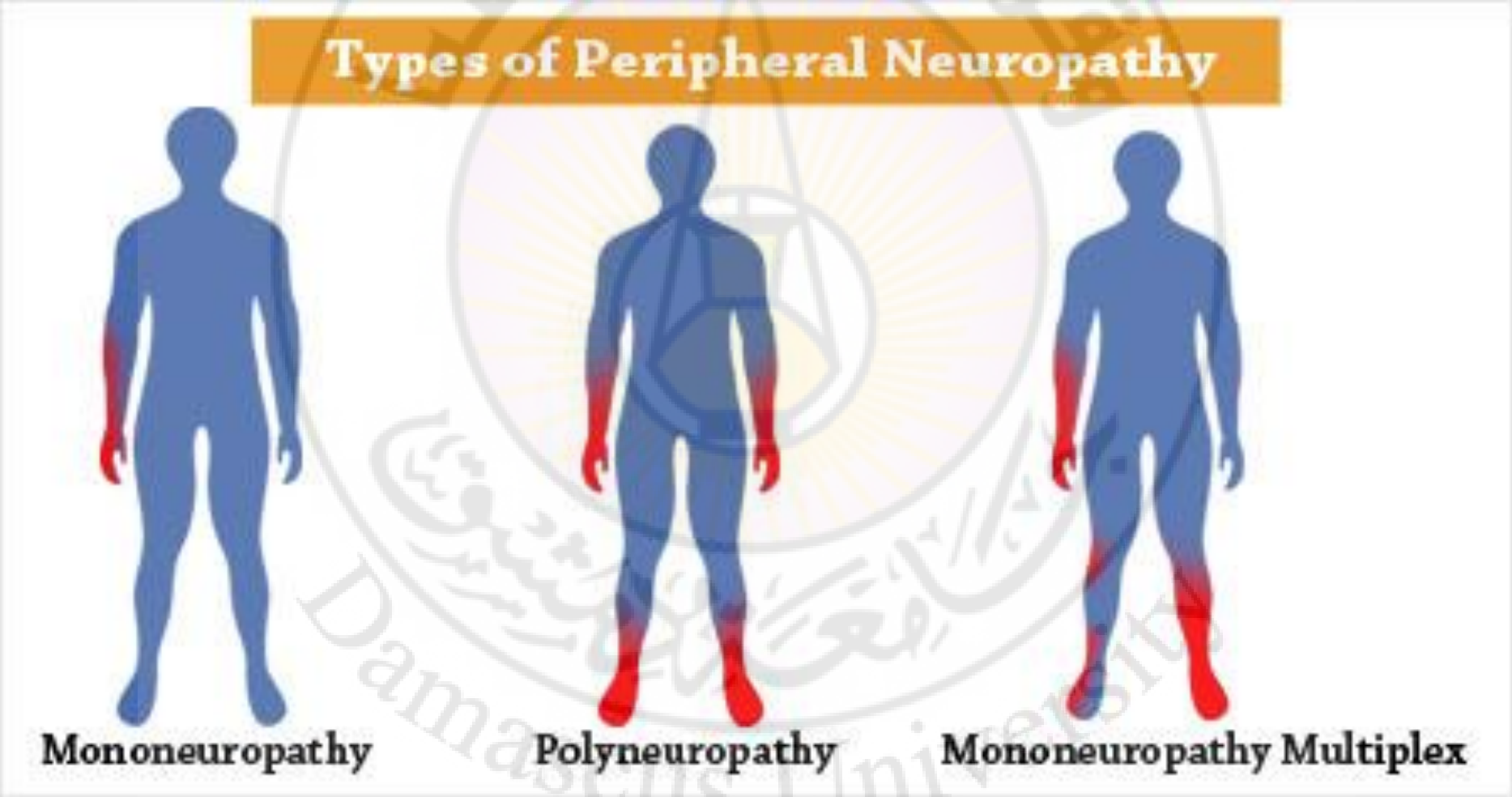
Dysarthria

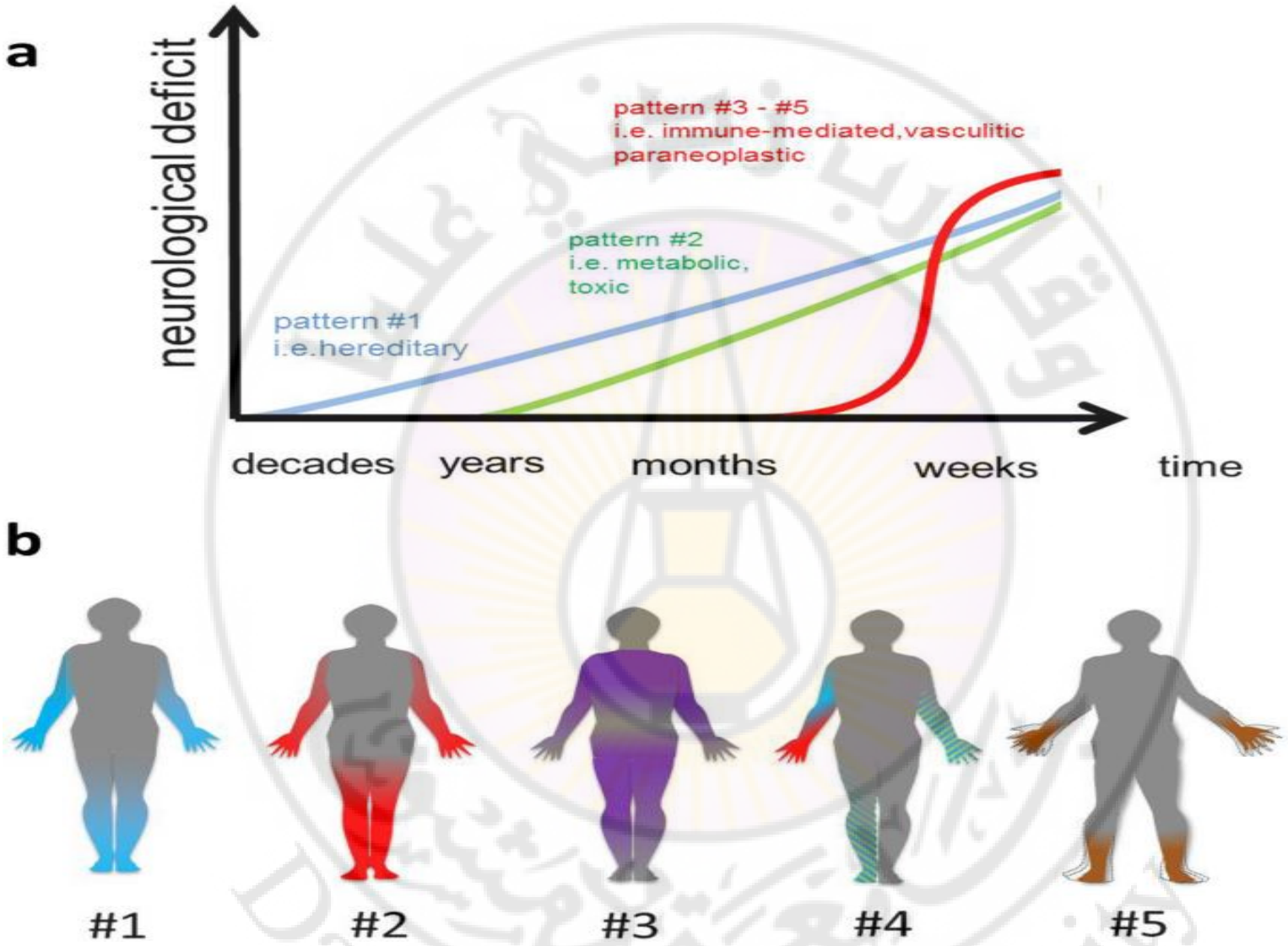
- Speech therapy often helpful early
- Computer technology offer many options to assist with patient communication

Peripheral neuropathy



Peripheral neuropathy





Disease onset and temporal evolution characteristics of distinguishable clinical patterns and different causes of peripheral neuropathy

Sensory deficits are drawn in blue

Motor deficits are drawn in red

Sensorimotor in magenta color

Painful and / or autonomous dysfunction is colored with green lines

Loss of proprioception is colored in brown

#1 is a distal symmetric predominantly sensory neuropathy

#2 a motor neuropathy with muscle wasting and foot abnormalities

#3 is characterized by proximal involvement of sensory and motor nerve fibers

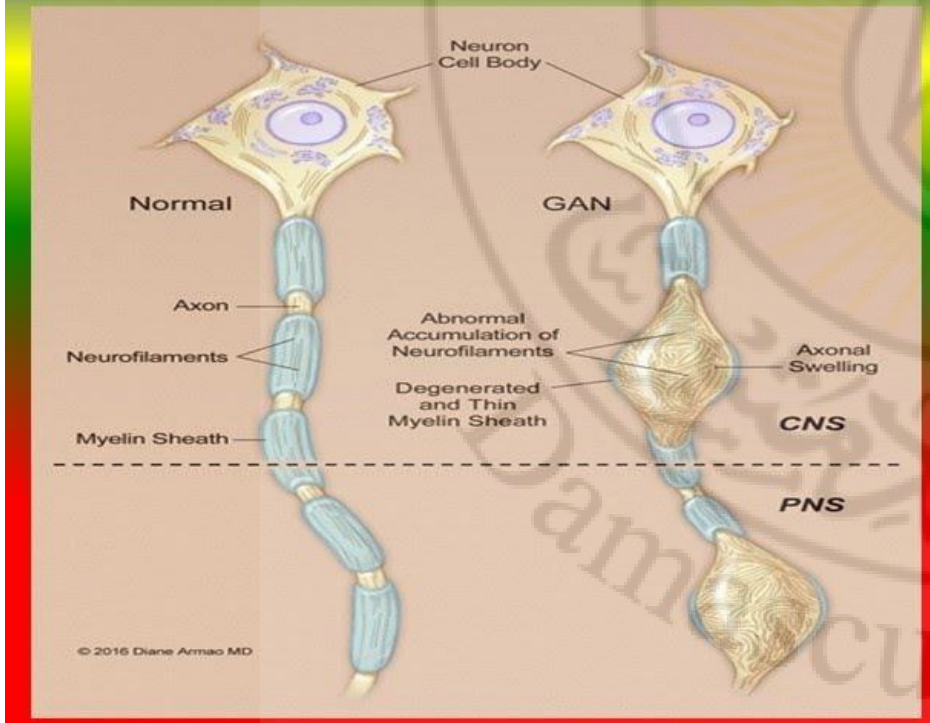
pattern #4 presents wih multifocal symptoms, neuropathic pain, and autonomic dysfunction

Pattern #5: is a sensory ataxic neuropathy

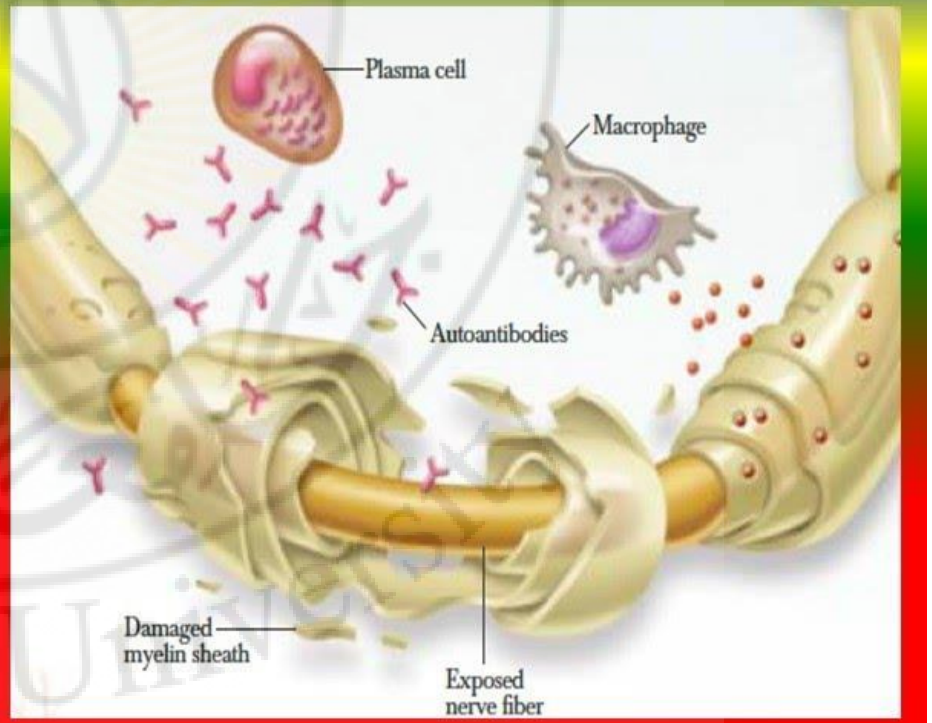
Peripheral neuropathy

Difference Between

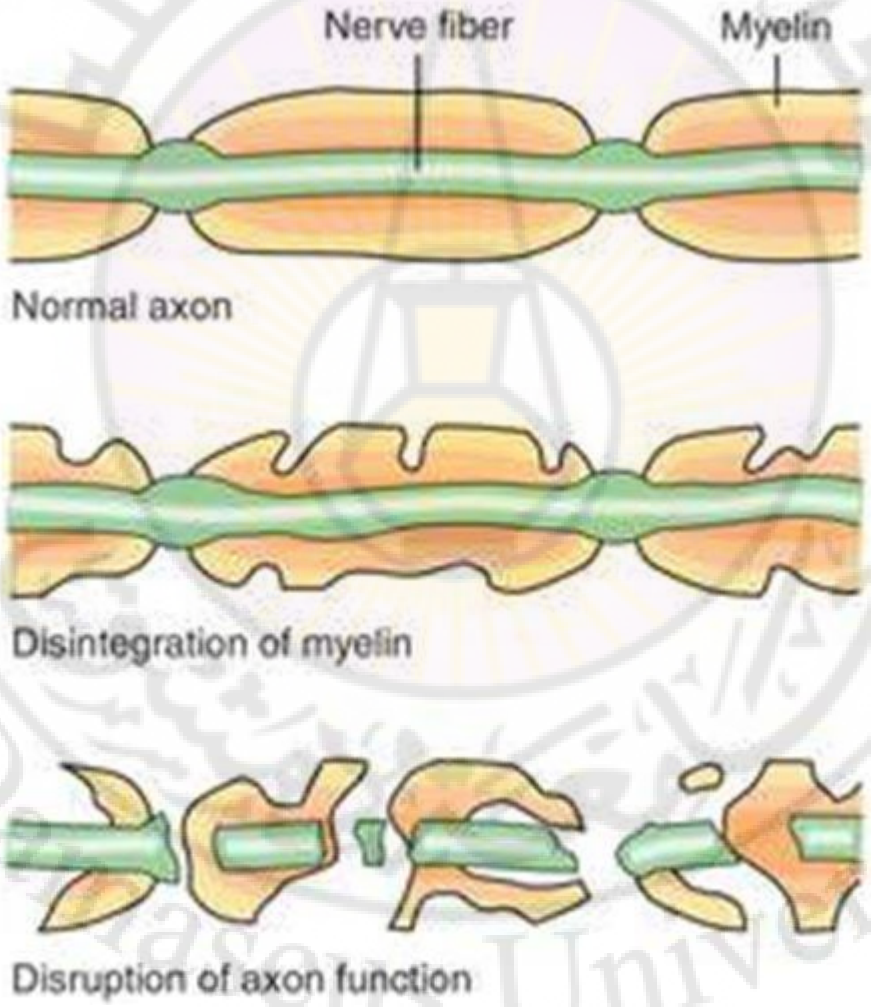
Axonal Neuropathy

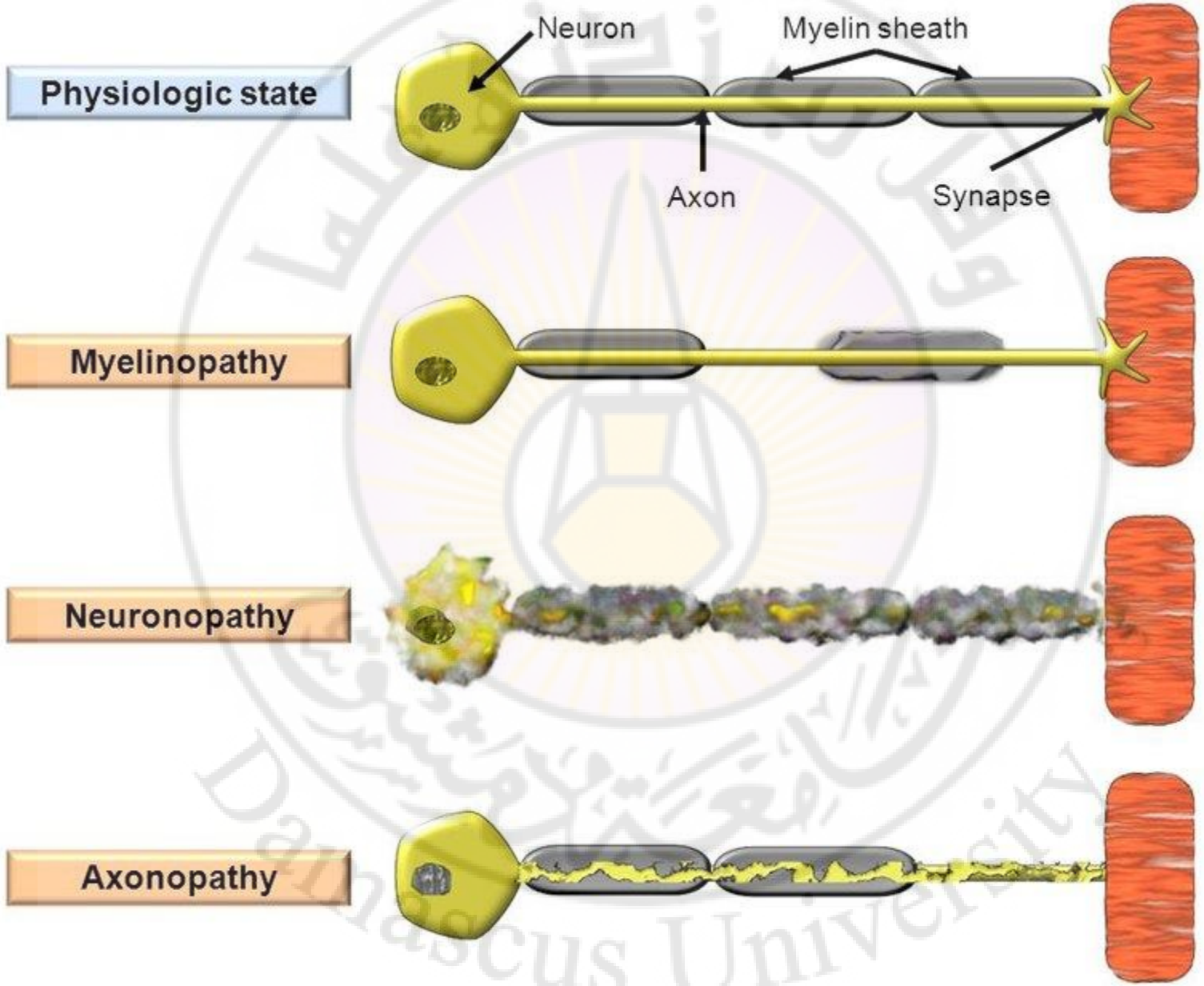


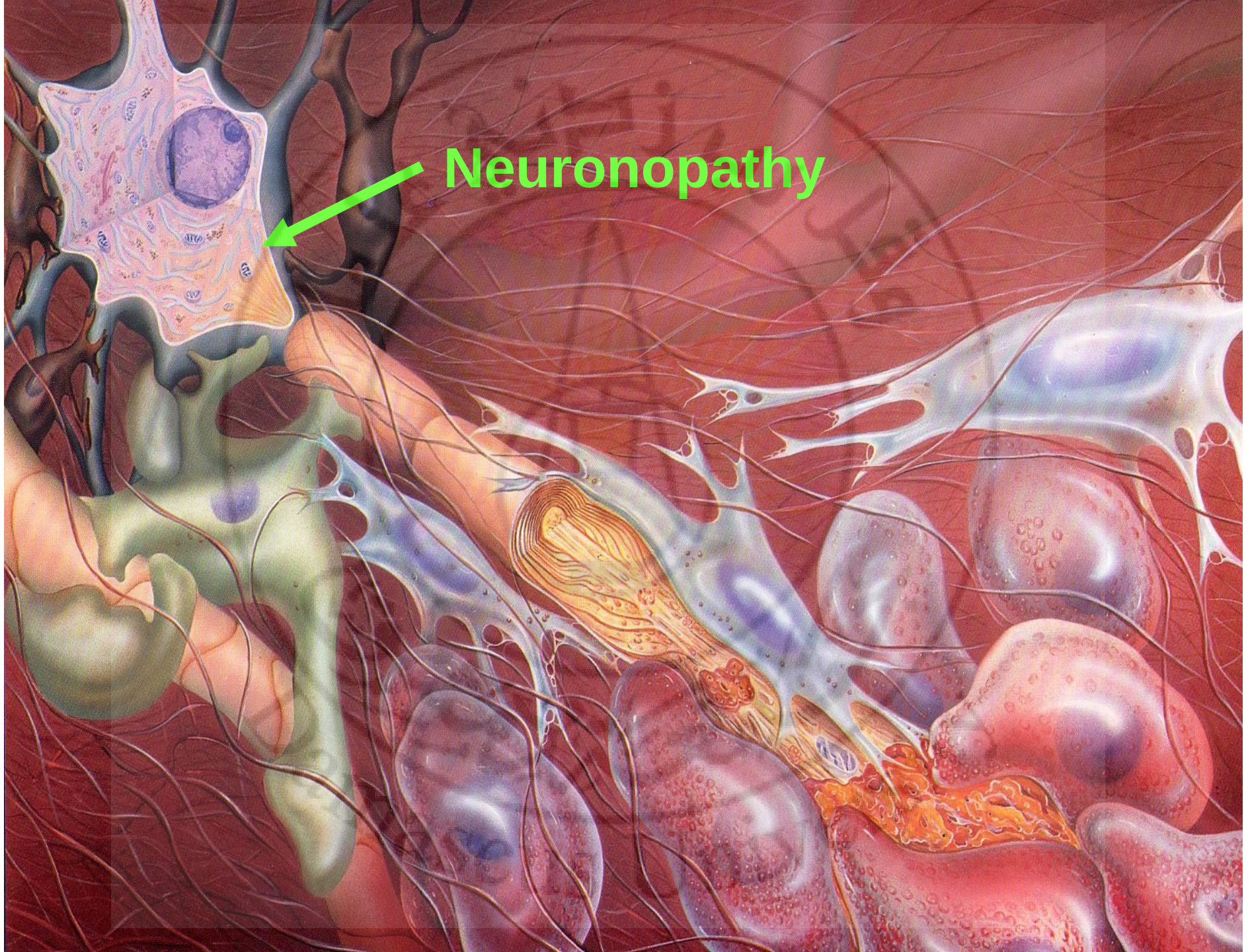
Demyelinating Neuropathy

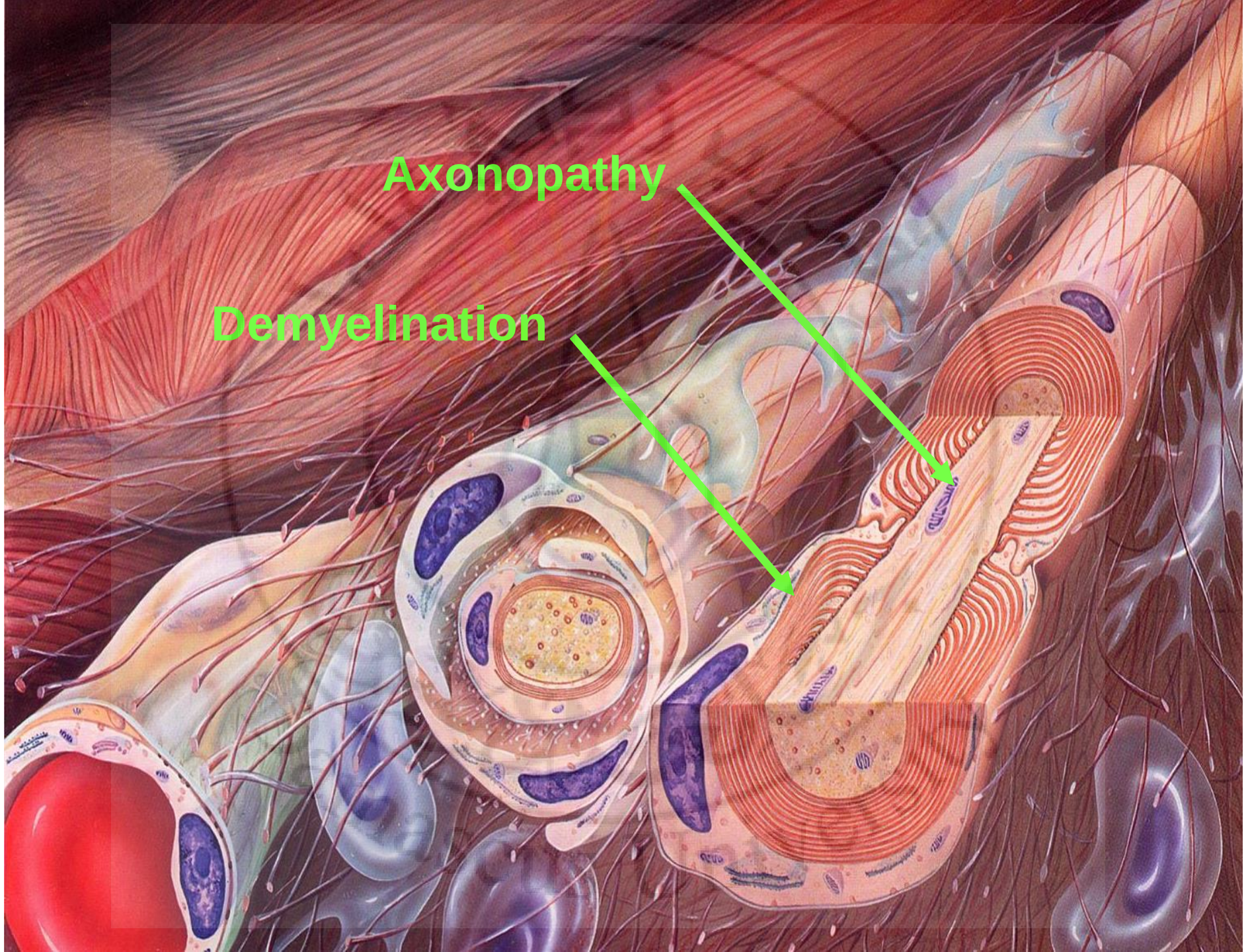


Peripheral neuropathy

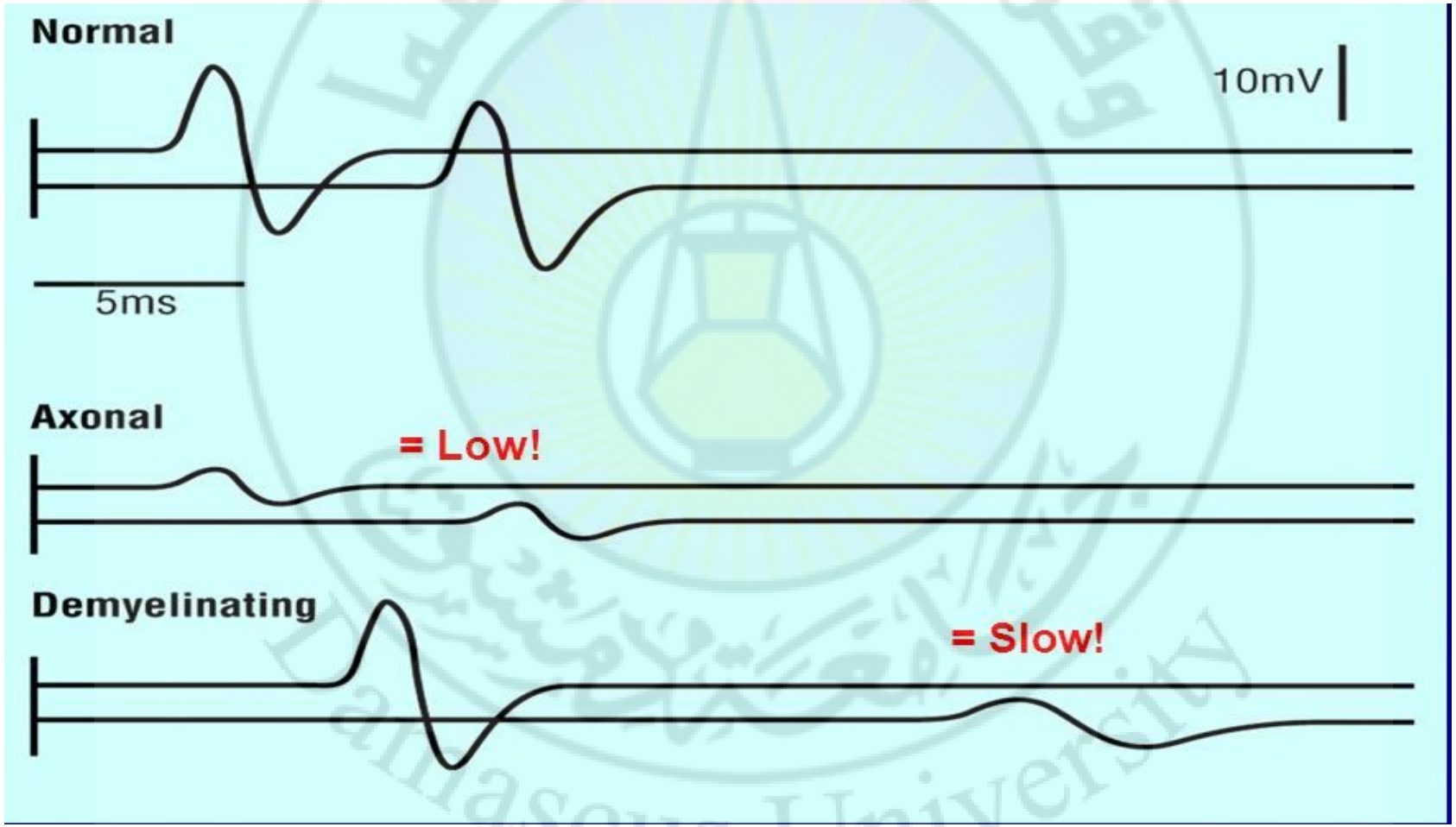



Physiologic state
Neuron
Myelin sheath
Axon
Synapse
Myelinopathy
Neuronopathy
Axonopathy

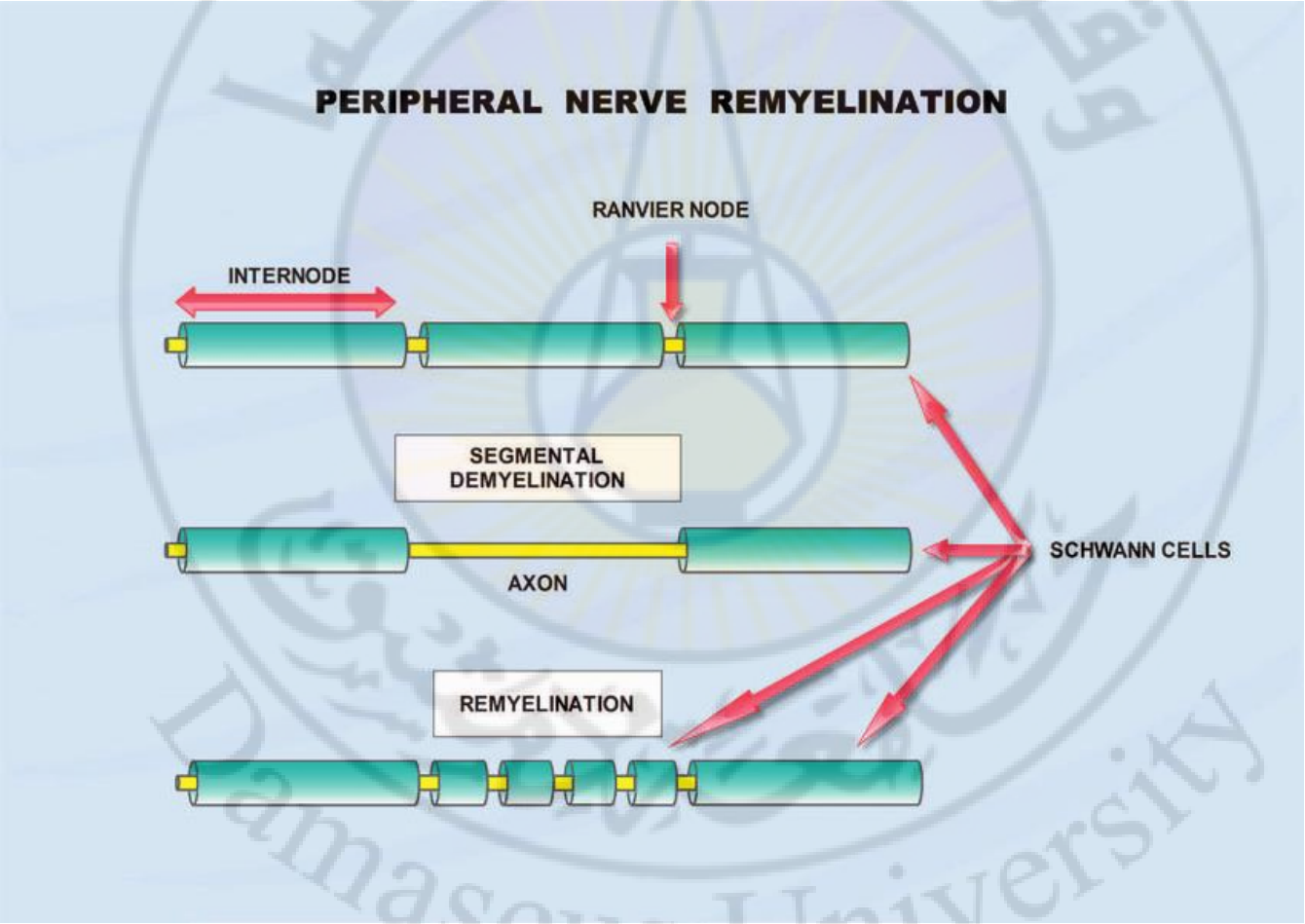

Neuronopathy


Axonopathy
Demyelination

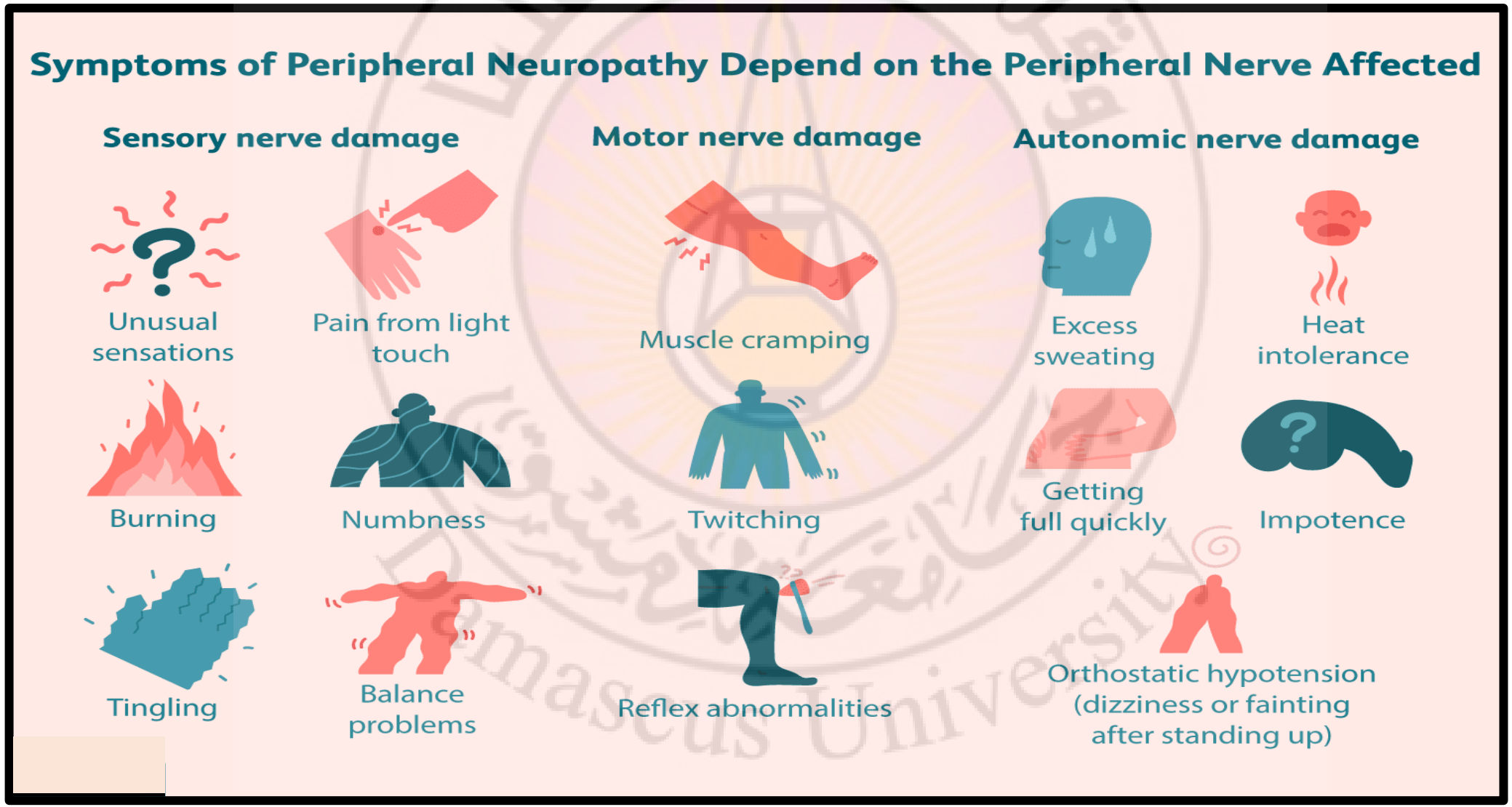
Peripheral neuropathy



Peripheral neuropathy



Peripheral neuropathy



Peripheral neuropathy

	Sensory	Motor	Reflex
Symptoms			
Upper limbs	Glove distribution of tingling, pins and needles and numbness	Weakness of grip and fingers	
	Difficulty in manipulating small objects in the fingers because of loss of sensation		
Lower limbs	Stocking distribution of tingling, pins and needles and numbness	Foot drop	
	Unsteadiness of stance and gait, especially in the dark or when eyes closed	Loss of spring at the ankles for running and climbing stairs	
Signs			
Upper limbs	Glove distribution of sensory loss, affecting any sensory modality	Distal lower motor neurone signs in hands	Loss of distal reflexes, e.g. supinator jerks
	Sensory ataxia in fingers and hands		
Lower limbs	Stocking distribution of sensory loss, affecting any sensory modality	Distal lower motor neurone signs in legs and feet	Loss of distal reflexes, especially ankle jerks
	Sensory ataxia in legs and gait		
	Rombergism (i.e. dependence on eyes for balance)		

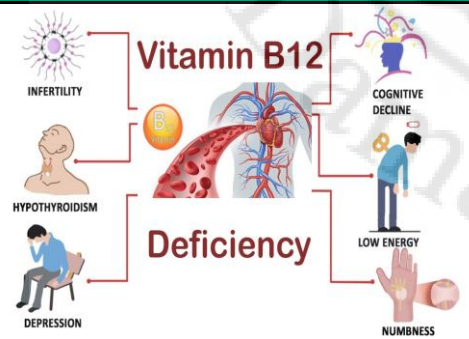
Peripheral neuropathy

Deficiency	Vitamin B_1 in alcoholics Vitamin B_6 in patients taking isoniazid Vitamin B_{12} in patients with pernicious anaemia and bowel disease
Toxic	Alcohol Drugs, e.g. isoniazid, vincristine, aminodarone
Metabolic	Diabetes mellitus Chronic renal failure
Inflammatory	Guillain–Barré syndrome Chronic inflammatory demyelinating polyneuropathy
Paraneoplastic	Bronchial carcinoma and other malignancies
Connective tissue disease	Rheumatoid arthritis Systemic lupus erythematosus Polyarteritis nodosa
Hereditary	Hereditary motor and sensory neuropathy (HMSN) (also known as Charcot–Marie–Tooth disease)
Haematological	Paraproteinaemia
Idiopathic	Perhaps accounting for 50% of cases

Peripheral neuropathy

In developed countries the commonest identifiable causes of peripheral neuropathy are alcohol and diabetes.

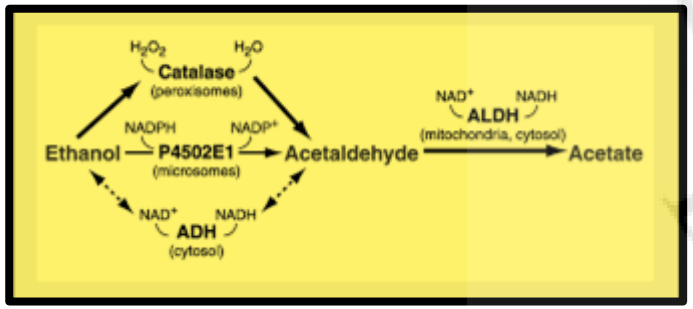
In other parts of the world, vitamin deficiency and leprosy cause more disease, although this is gradually changing

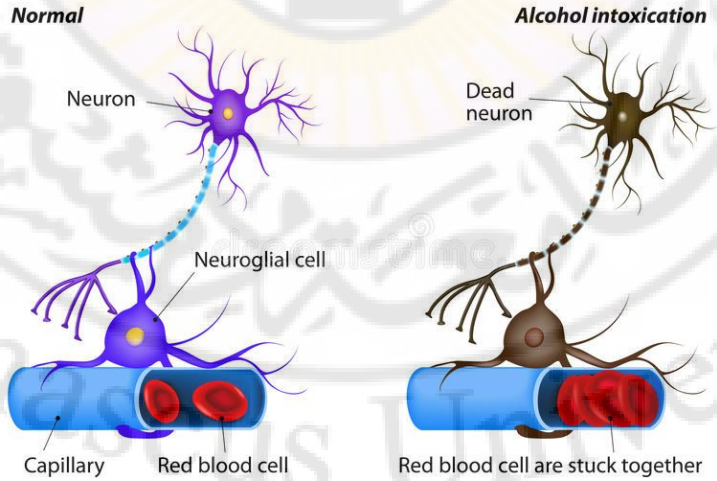


Peripheral neuropathy

Alcoholic neuropathy

Alcoholic neuropathy is common and usually more sensory than motor. How much it is caused by the direct toxic effect of alcohol on the peripheral nerves, and how much it is due to coexistent vitamin B1 deficiency, is not completely known.





A genetic predisposition for some alcoholics that results in increased frequency of alcoholic polyneuropathy in certain ethnic groups

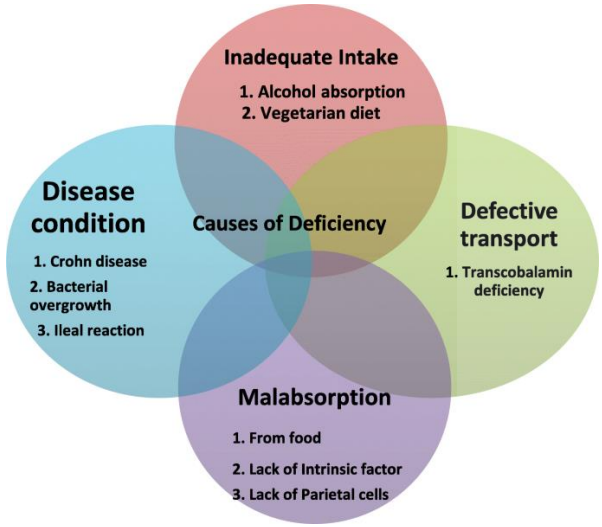
Peripheral neuropathy

CLINICAL GEMS

Avoid nitrous oxide anesthesia in anyone at risk of vitamin B_{12} deficiency

Vitamin B_{12} deficiency

Vitamin B_{12} deficiency is not a common cause of neuropathy, but is an important one to recognize because of its reversibility.
Every effort should be made to reach the diagnosis before the irreversible changes of subacute combined degeneration of the spinal cord become established.



Mental Problems
Problems such as brain fog, Alzheimer's and dementia are symptoms of low B12

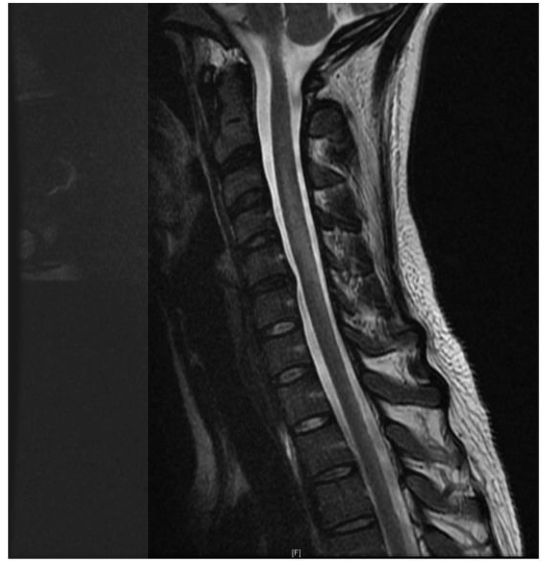
Fatigue
The most classic B12 Deficiency symptom

Hair Problems
Thinning hair and grey hair can be symptoms too

Chronic Pain
Fibromyalgia, back pain, neuropathy and more

Infertility
In both men and women

Blood Disorders
Blood disorders such as elevated MCV are symptoms

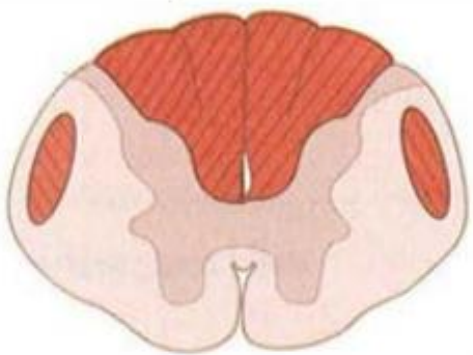


Peripheral neuropathy

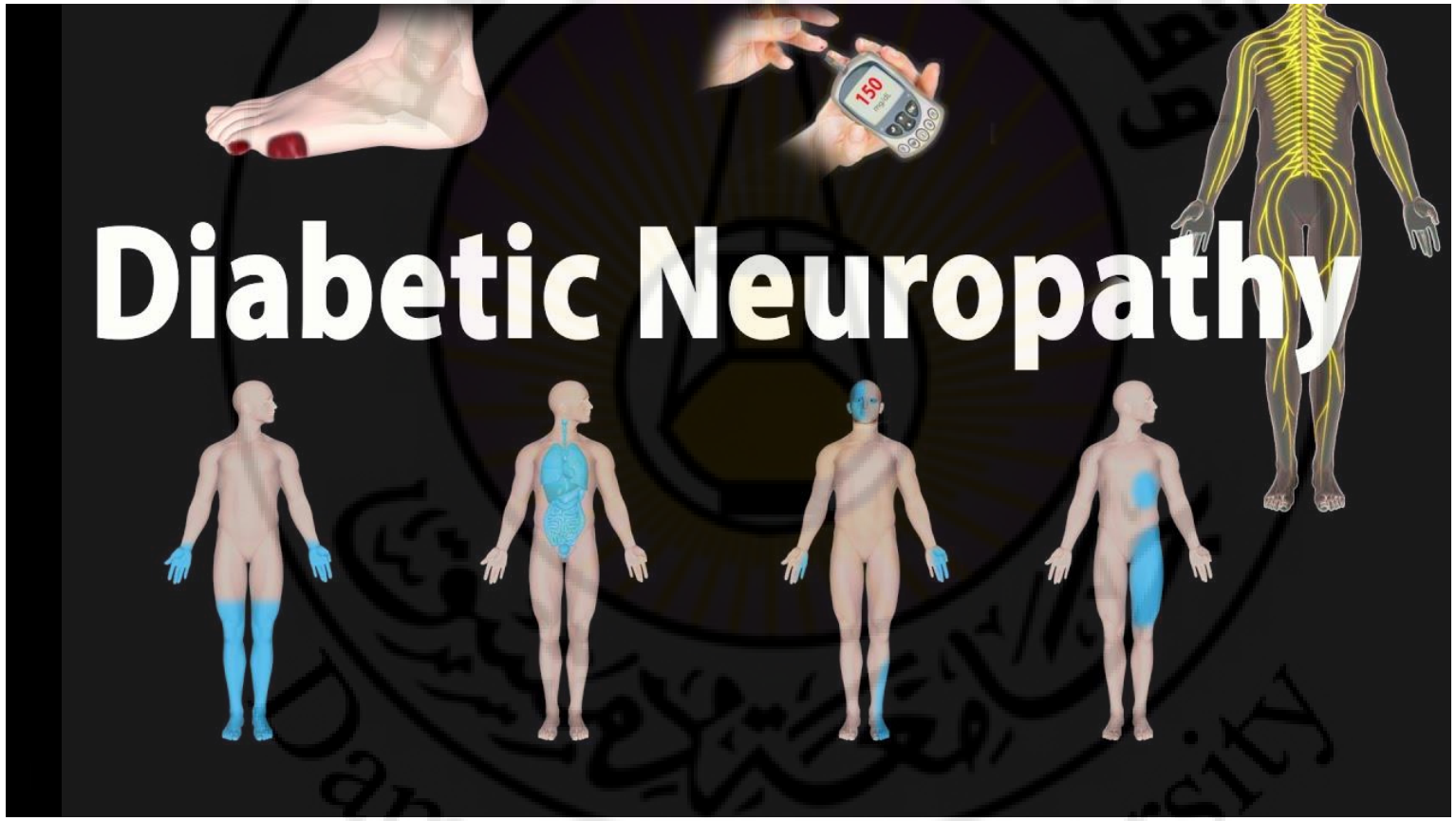
Subacute combined degeneration of the cord

Cause	B12 deficiency (usually pernicious anaemia)
Pathology	Degeneration of the dorsal columns (myelin degeneration)
Signs & symptoms	• Legs, arms, trunk – progressive from tingling and numbness to weakness • Visual impairment • Change in mental state • BILATERAL spastic paresis/paralysis • Sensations diminished = pressure, vibration and touch
Clinical tests	• +ve Babinski sign = extensor plantar reflex • +ve Rhomberg test
Treatment	Reversible with B12 replacement if not been going on for too long

Vitamin B_{12} neuropathy and Friedreich´s ataxia: demyelination of dorsal columns, lateral corticospinal tracts, and spinocerebellar tracts; ataxic gait, hyperreflexia, impaired position and vibration sense



Peripheral neuropathy



Diabetic Neuropathies

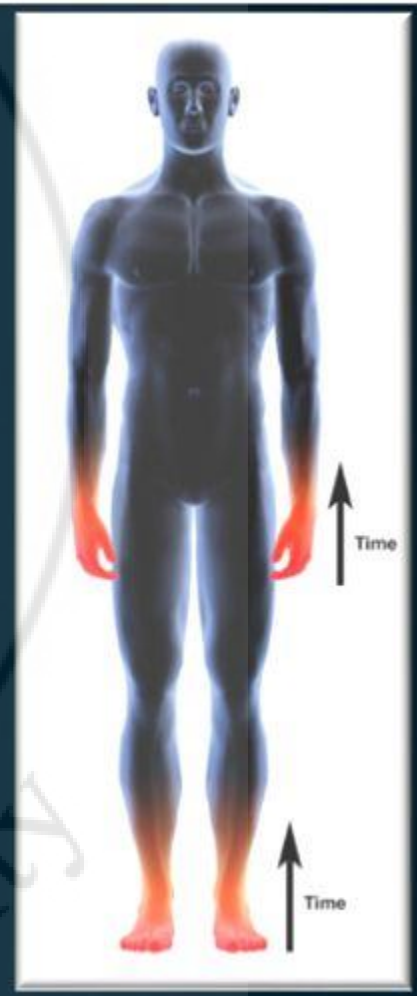
Symptoms and Signs of Diabetic Peripheral Neuropathy

Symptoms
Small Fiber

- Numbness or loss of feeling (asleep or "bunched up sock under toes" sensation)
- Prickling/Tingling
- Aching Pain
- Burning Pain
- Lancinating Pain
- Allodynia
- Defective Thermal Sensation
- Decreased Sweating

Signs
Large Fiber

- Diminished vibratory perception
- Decreased knee and ankle reflexes
- Reduced protective sensation such as pressure, hot and cold, pain
- Diminished ability to sense position of toes and feet
- Pain is deep, aching or cramping



Symptoms and signs progress from distal to proximal over time

Boulton AJ, et al. *Diabetes Care*. 2005 April; 28(4):956-62.

Peripheral neuropathy

DPN Produces Positive and Negative Symptoms

- Positive Symptoms
  - Spontaneous Pain
  - Dysesthesias
    - C-Fibers
    - Unpleasant
  - Parasthesias
    - A-Fibers
    - Not Unpleasant
- Negative Symptoms
  - Loss/impairment of sensory quality
  - Numbness
  - Dry skin
  - Erectile dysfunction
  - Incontinence
  - Gait instability and fall risk

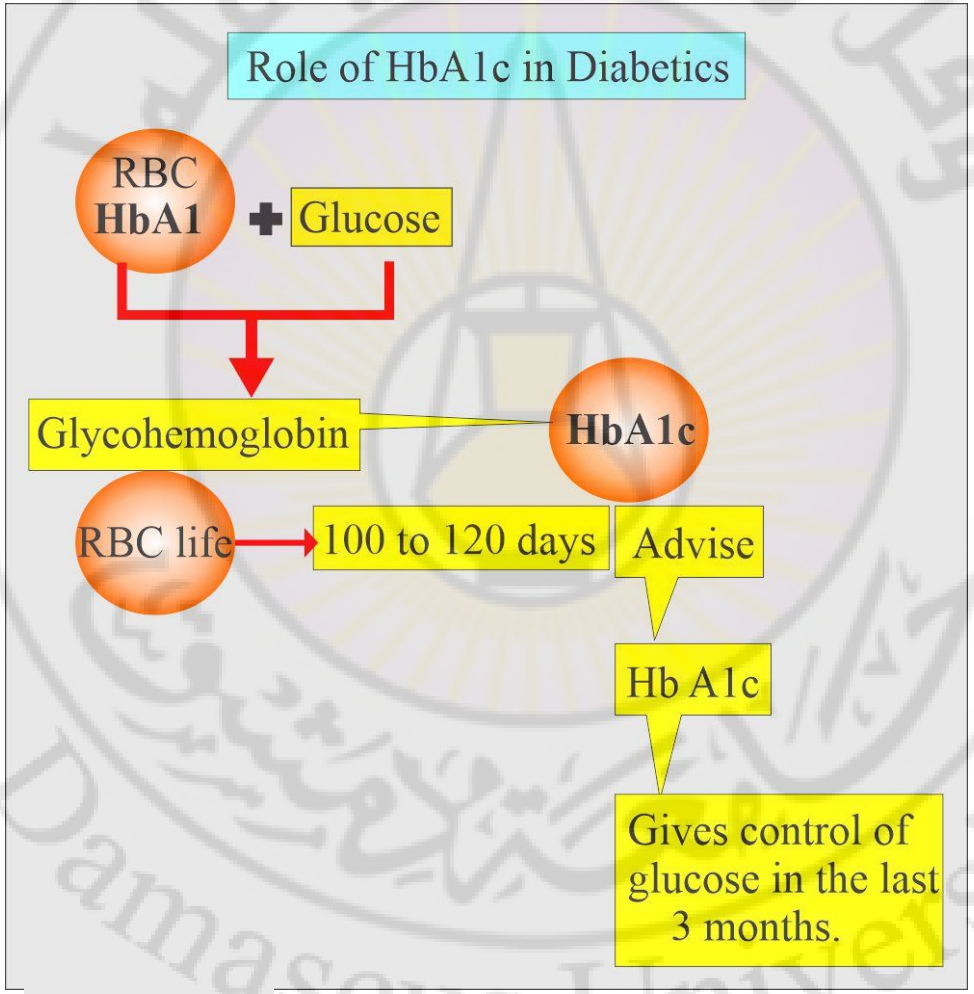
Baron R. *Clin J Pain.* 2000;16(2 suppl):S12-S20.

TABLE 1: CHARACTERIZATION OF NEUROPATHIC PAIN

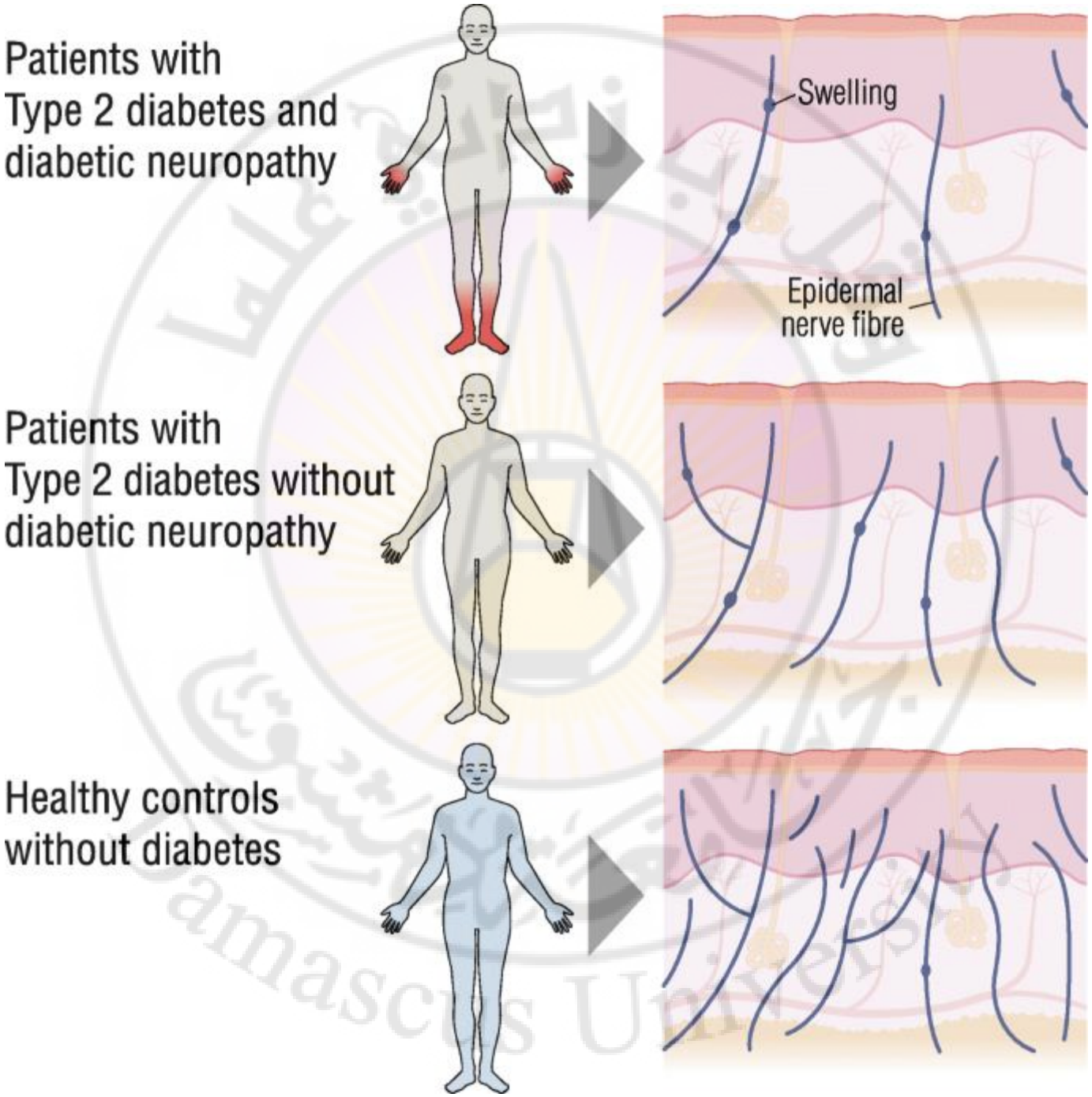
Negative Symptoms	Definition
Hypoesthesia	Reduced perception of nonpainful stimuli
Hypoalgesia	Reduced perception of painful stimuli
Thermo hypoesthesia	Reduced perception of heat
Positive Symptoms	
Spontaneous Pain	
Paresthesias	Nonpainful tingling sensation
Paroxysmal pain	Shooting pain that occurs intermittently for seconds at a time
Superficial pain	Continuous burning sensation
Stimulus-Induced Pain	
Allodynia	Pain induced by a typically nonpainful moving stimuli on the skin
Hyperalgesia	Pain induced by a typically nonpainful static stimuli on the skin
Summation	Increasing amount of pain due to a typically nonpainful repetitive stimuli

Diabetic Neuropathies

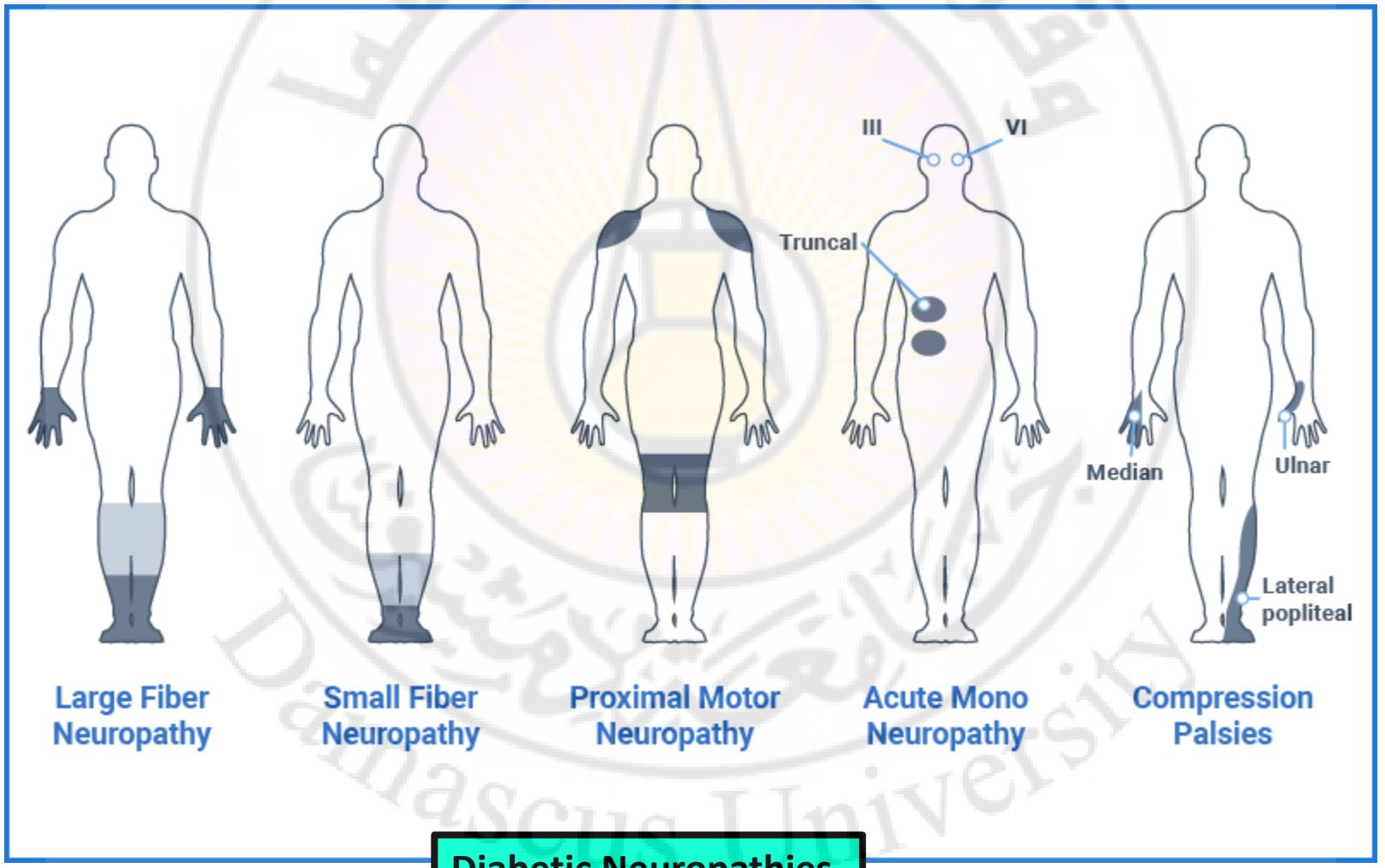
Peripheral neuropathy



Diabetic Neuropathies

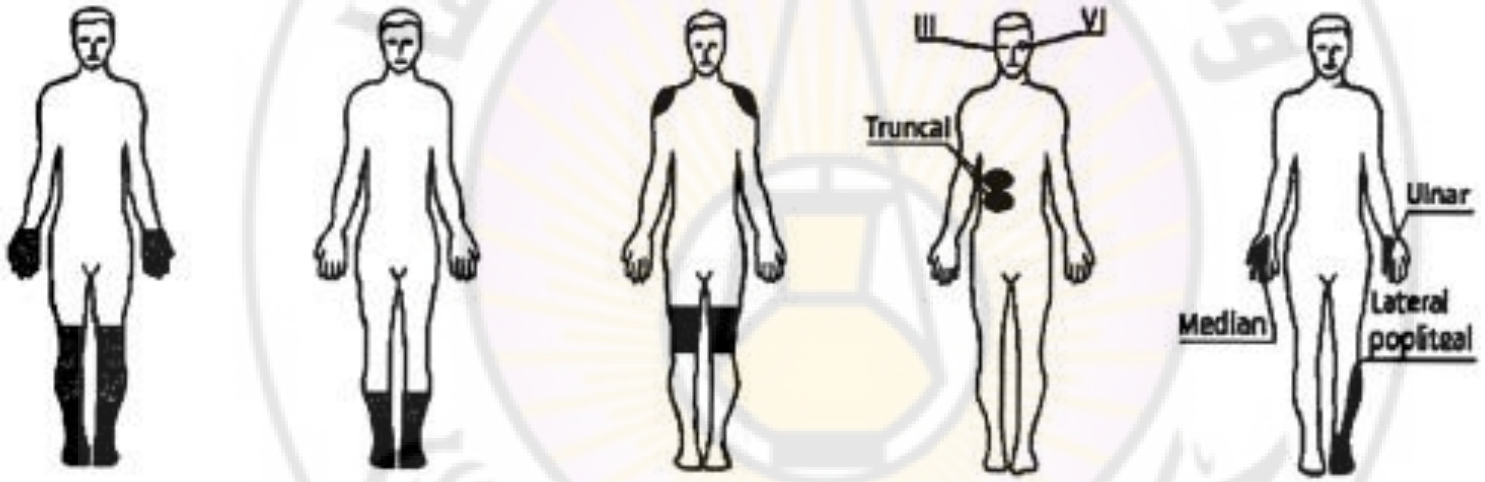

Patients with
Type 2 diabetes and
diabetic neuropathy
Swelling
Epidermal
nerve fibre
Patients with
Type 2 diabetes without
diabetic neuropathy
Healthy controls
without diabetes

Peripheral neuropathy



Diabetic Neuropathies

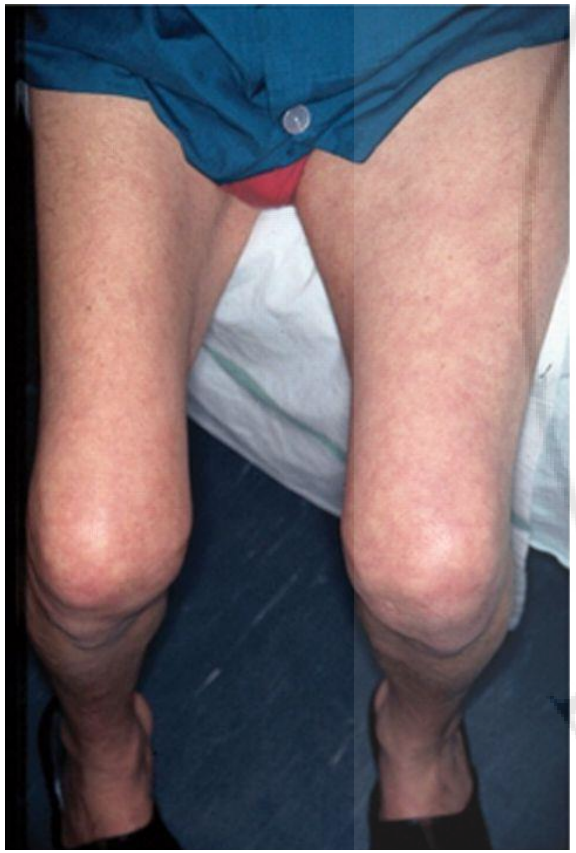
Peripheral neuropathy

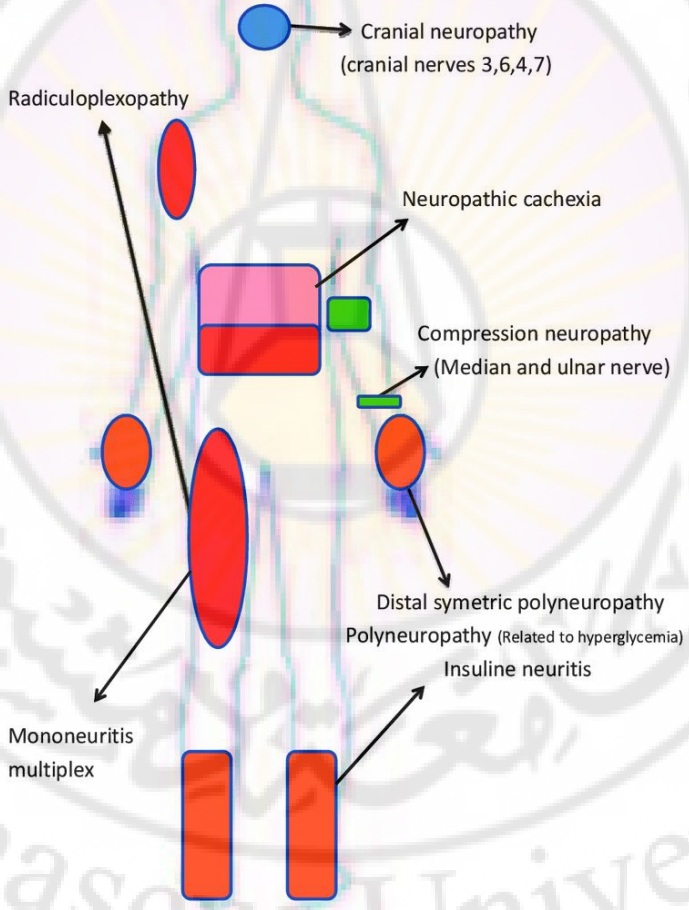


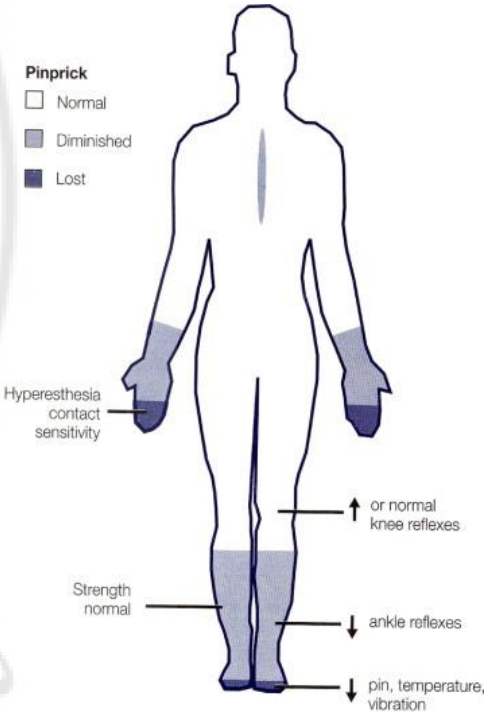
Large fiber Neuropathy	Small fiber Neuropathy	Proximal motor Neuropathy	Acute mono Neuropathies	Pressure Palsies
Sensory loss: 0→ +++ (Touch, vibration) Pain: + → +++ Tendon reflex: N → ↓↓↓ Motor deficit 0 → +++	Sensory loss: 0 → + (thermal , allodynia) Pain: + → +++ , Tendon reflex: N → ↓ Motor deficit: 0	Sensory loss: 0 → + Pain: + → +++ Tendon reflex: ↓↓ Proximal Motor deficit: + → +++.	Sensory loss: 0 → + Pain: + → +++ Tendon reflex: N Motor deficit: + → +++	Sensory loss in Nerve distribution: + → +++ Pain: + → ++ Tendon reflex: N Motor deficit: + → +++

Diabetic Neuropathies

Peripheral neuropathy

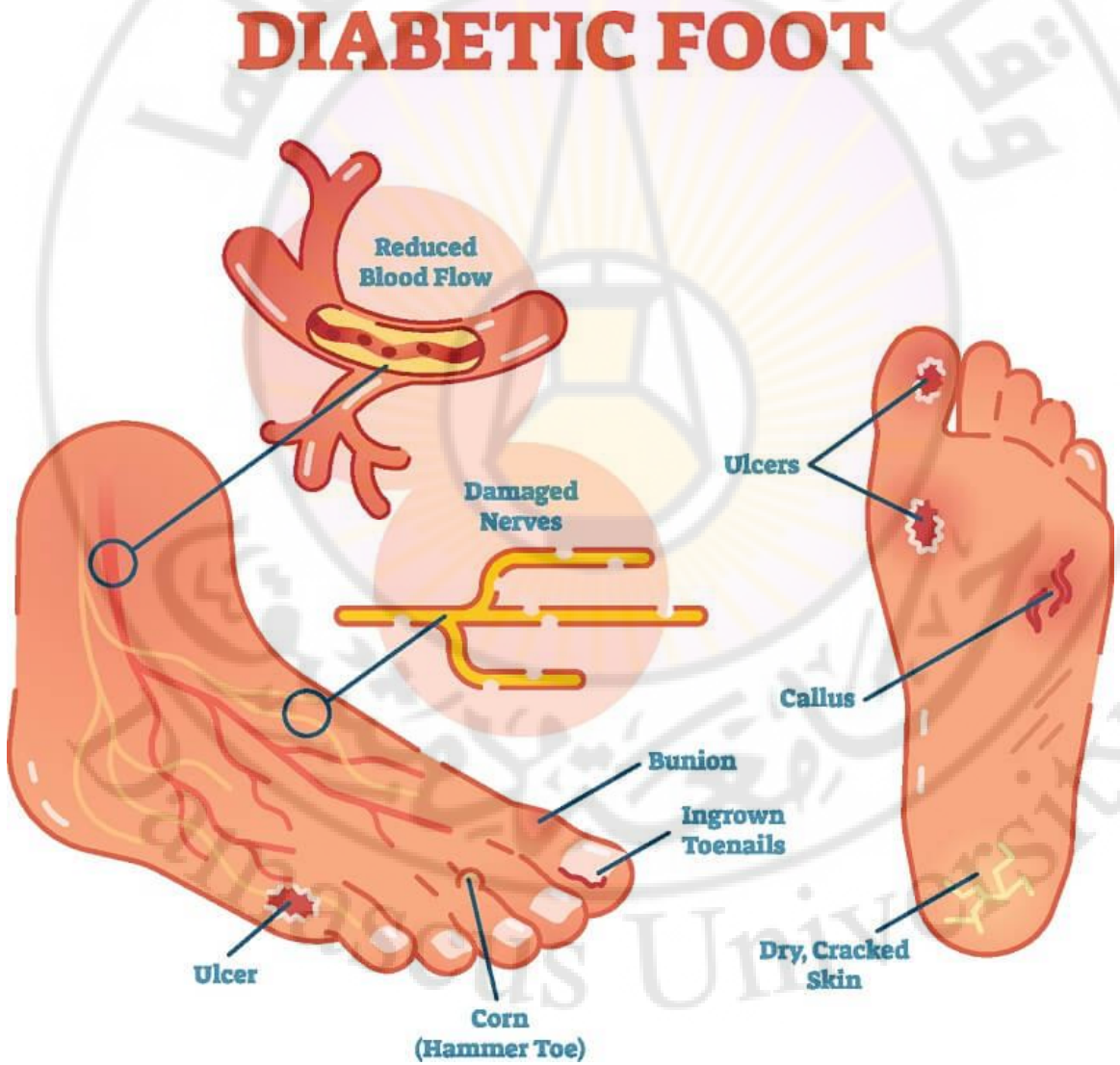






Diabetic Neuropathies

Peripheral neuropathy



Guillain–Barré syndrome

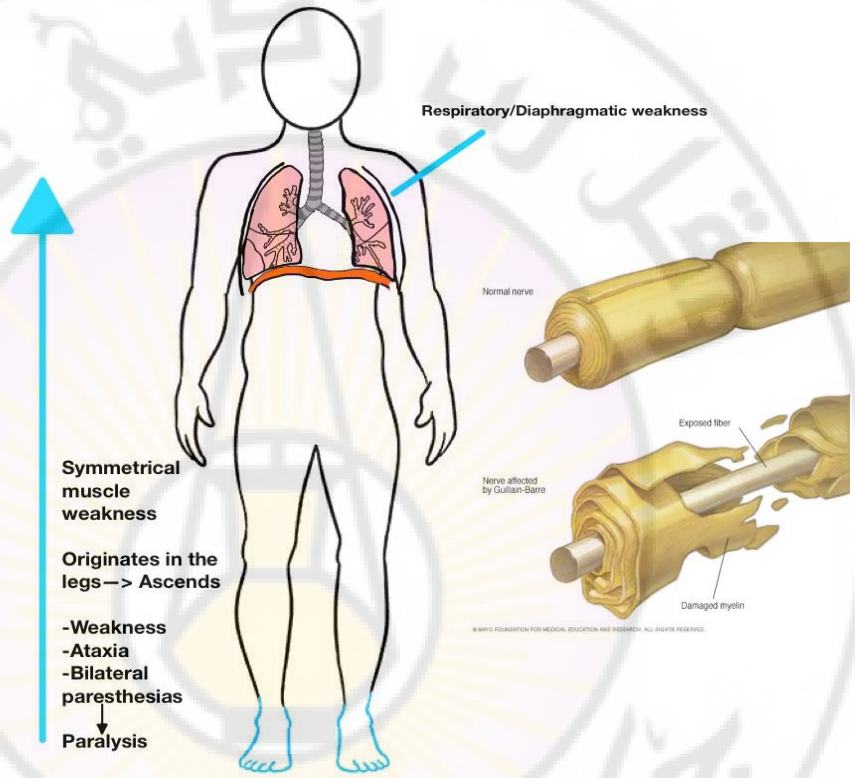
Acute AIDP that presents with rapidly progressive flaccid weakness

Epidemiology:
1-2 cases/100,000 per year
Slightly greater in males than females

Pathophysiology:
Immune response preceding infection
-Infection:
-Campylobacter jejuni
-HIV
-Influenza like illnesses
-CMV
-EBV
-COVID 19
-Zika virus
-Vaccination (flu, meningococcal, H1N1)

Clinical Manifestations:
-Fairly symmetric muscle weakness
-Absent or depressed DTR's
-Onset: Few days to a week
-Weakness: mild difficulty with walking to nearly complete paralysis of all extremity, facial, respiratory and bulbar muscles

Miller Fisher Syndrome:
-Opthaloplegia
-Ataxia
-Areflexia



Clinical features:
WEAKNESS: Starts in legs and ascends usually
Can begin in arms or face (10% of patients)
RESPIRATORY MUSCLE WEAKNESS: May require ventilator support (10-30%)
FACIAL NERVE PALSIES/OROPHARYNGEAL WEAKNESS
OCULOMOTOR WEAKNESS
DECREASED/ABSENT REFLEXES: Arms or legs
PARASTHESIAS: Hands or feet
PAIN: Due to nerve root inflammation. Back or extremities
DYSAUTONOMIA: Life threatening labile BP and arrythmias
-Diarrhea/constipation -hyponatremia - bradycardia
-urinary retention -tachycardia -reversible cardiomyopathy
-Horner syndrome -Sudden death

DIAGNOSIS:
CSF:
- CSF PROTEIN
- NORMAL CSF WBC
(Albuminocytoligic dissociation)

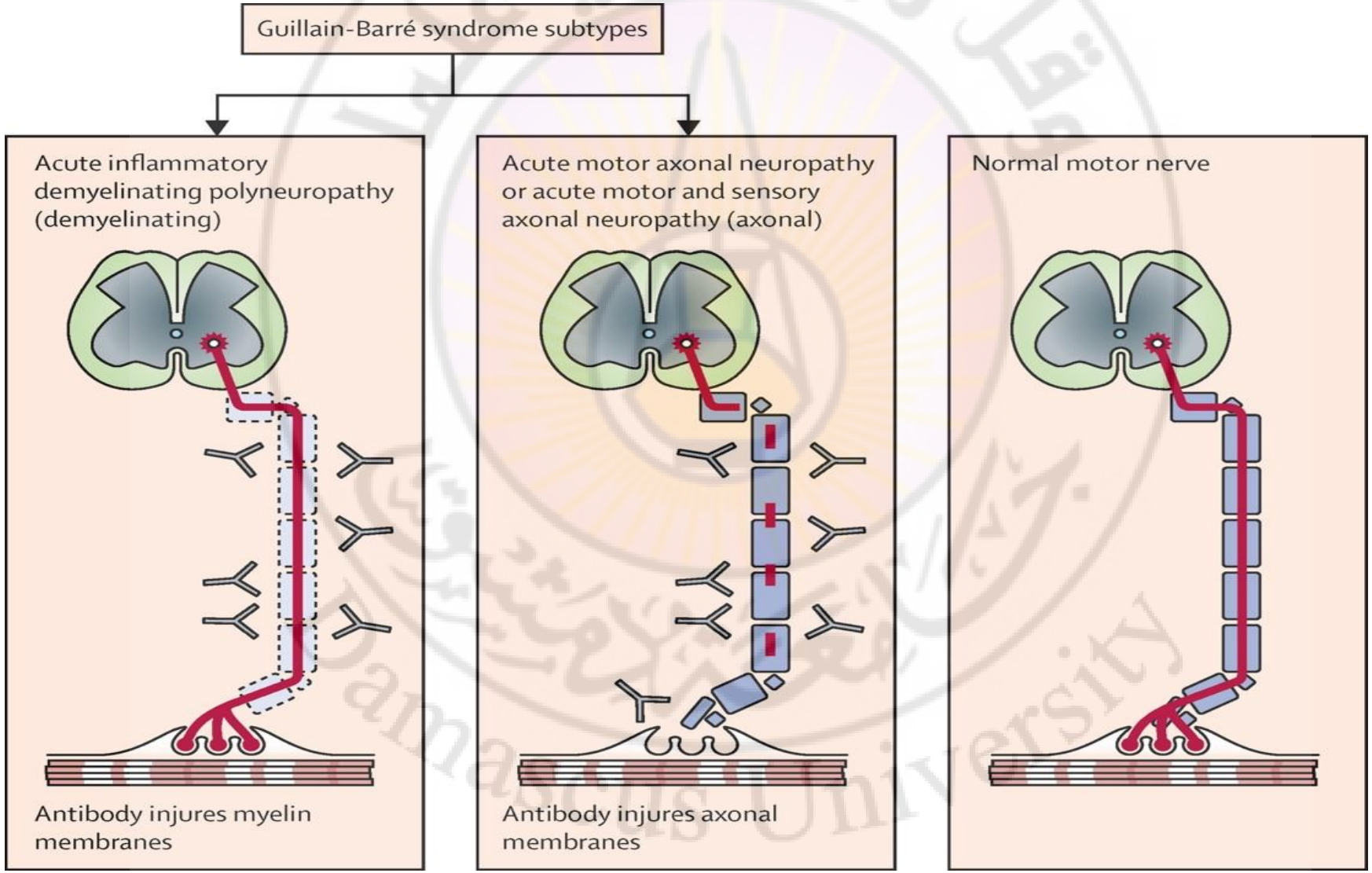
Electrodiagnostic studies:
-EMG NCV can classify the main variants:
(1) acute polyneuropathy with demyelination features
(2) axonal form

MRI:
-Thickening and enhancement of intrathecal spinal nerve roots and cauda equina

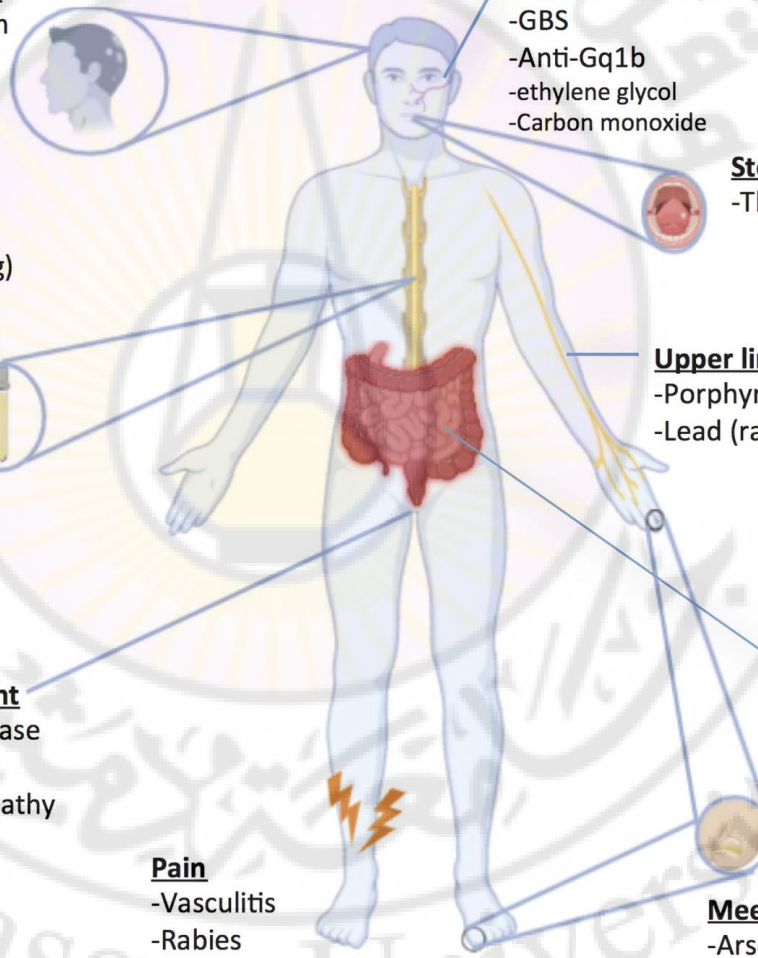
GQ1b IgG Antibody
associated with Miller Fisher Variant.

TREATMENT:
-Plasmapharesis + IVIG
-Mechanical ventilation
-Steroids contraindicated-worse outcome

Peripheral neuropathy



Peripheral neuropathy



Alopecia
-Thallium
-Arsenic
-Mercury
-Selenium
-Colchicine

Bilateral facial palsy
-GBS
-Anti-Gq1b
-ethylene glycol
-Carbon monoxide

Stomatitis
-Thallium (riboflavin-related)

CSF Pleocytosis
-Malignant cells
-Adenocarcinoma(breast, lung)
-Melanoma
-Haematological malignancies
-Infectious meningitis
-TB
-Cryptococcus
-Syphilis
-Inflammatory diseases
-SLE
-HIV

Upper limb predominance
-Porphyria
-Lead (radial neuropathy)

Abdominal Symptoms
-Porphyria
-Various toxins
(thallium, arsenic)

Sphincter Involvement
-Leptomeningeal disease
-CMV
-Concomitant myelopathy

Pain
-Vasculitis
-Rabies
-CMV
-Malignant infiltration
-Parasitic infection
-Ciguatera

Mee's lines
-Arsenic
-Thallium

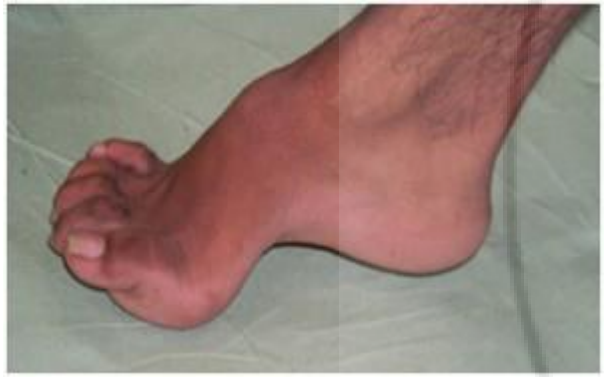
Peripheral neuropathy

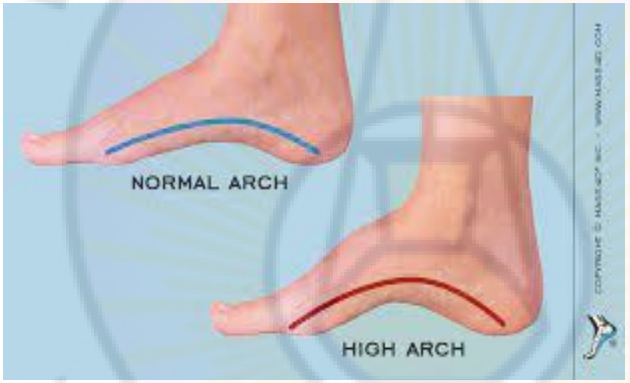
Hereditary motor and sensory neuropathy
(HMSN, also known as Charcot–Marie–Tooth disease)

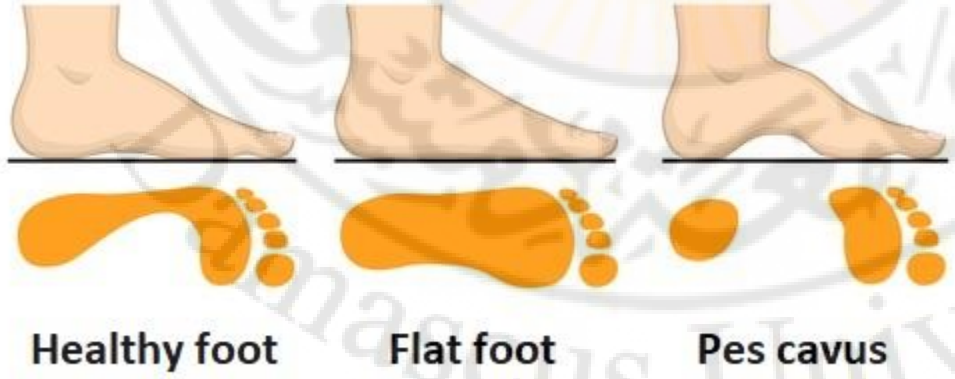
Key features of HMSN

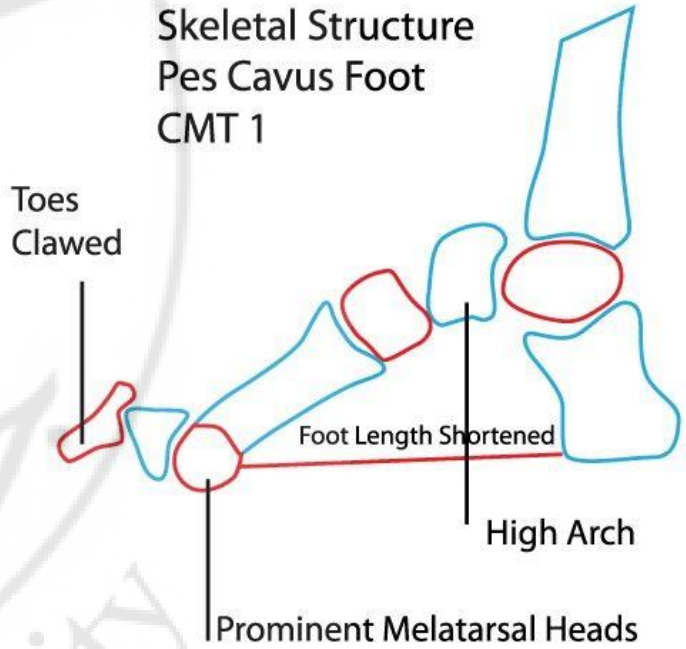
- Pes cavus
- Distal wasting ('champagne bottle legs')
- Distal weakness
- Absent reflexes
- Mild distal sensory loss

Peripheral neuropathy

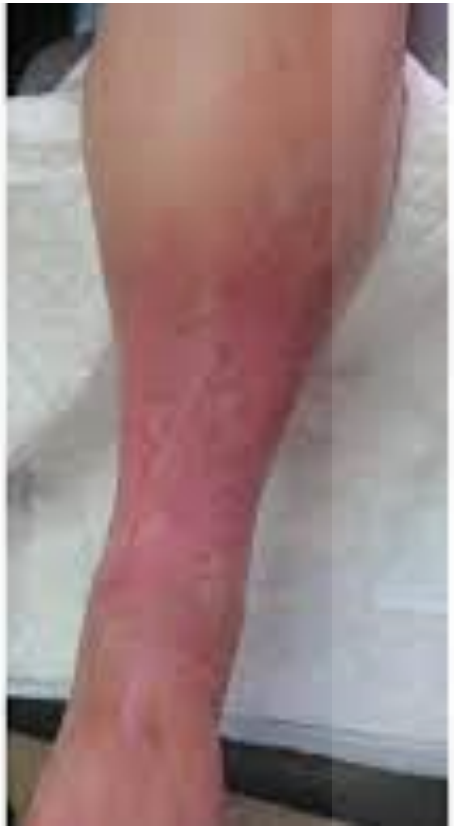




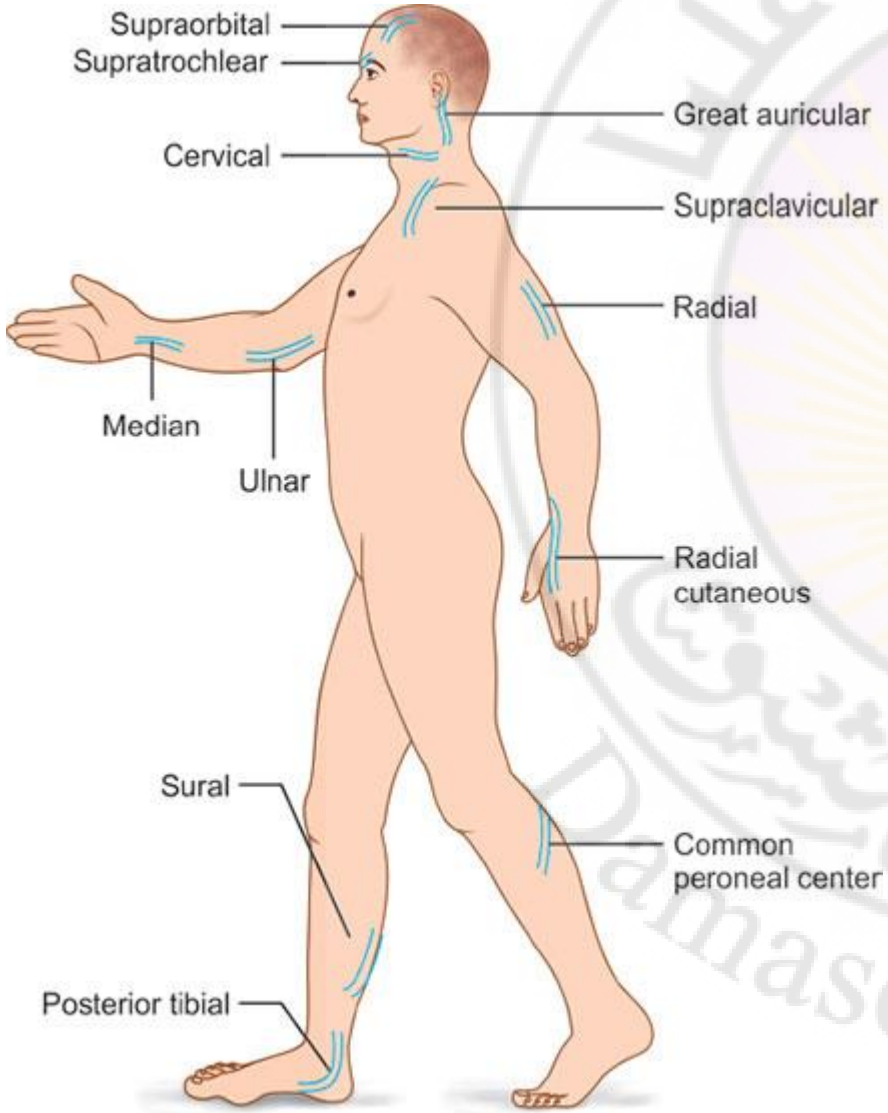




Peripheral neuropathy

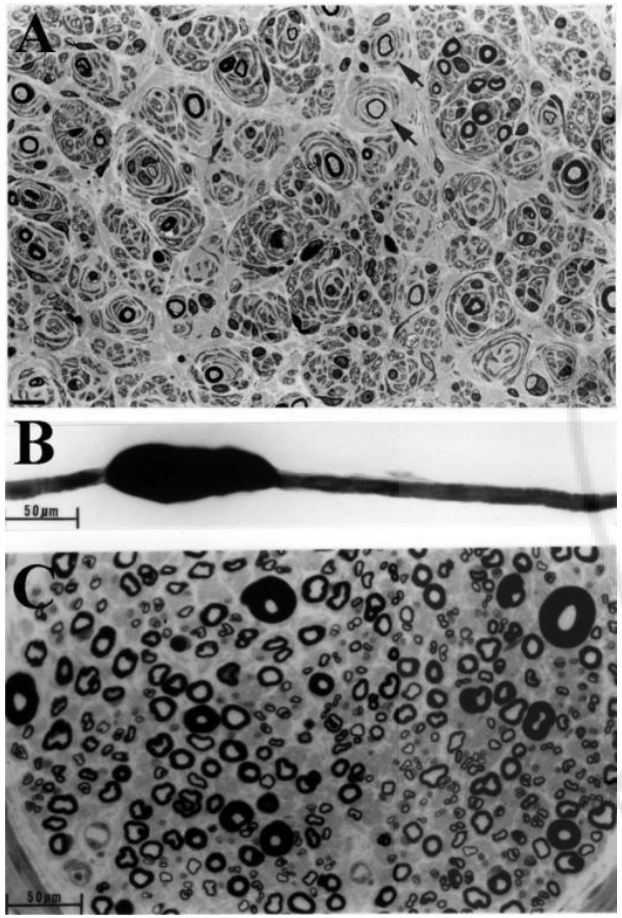


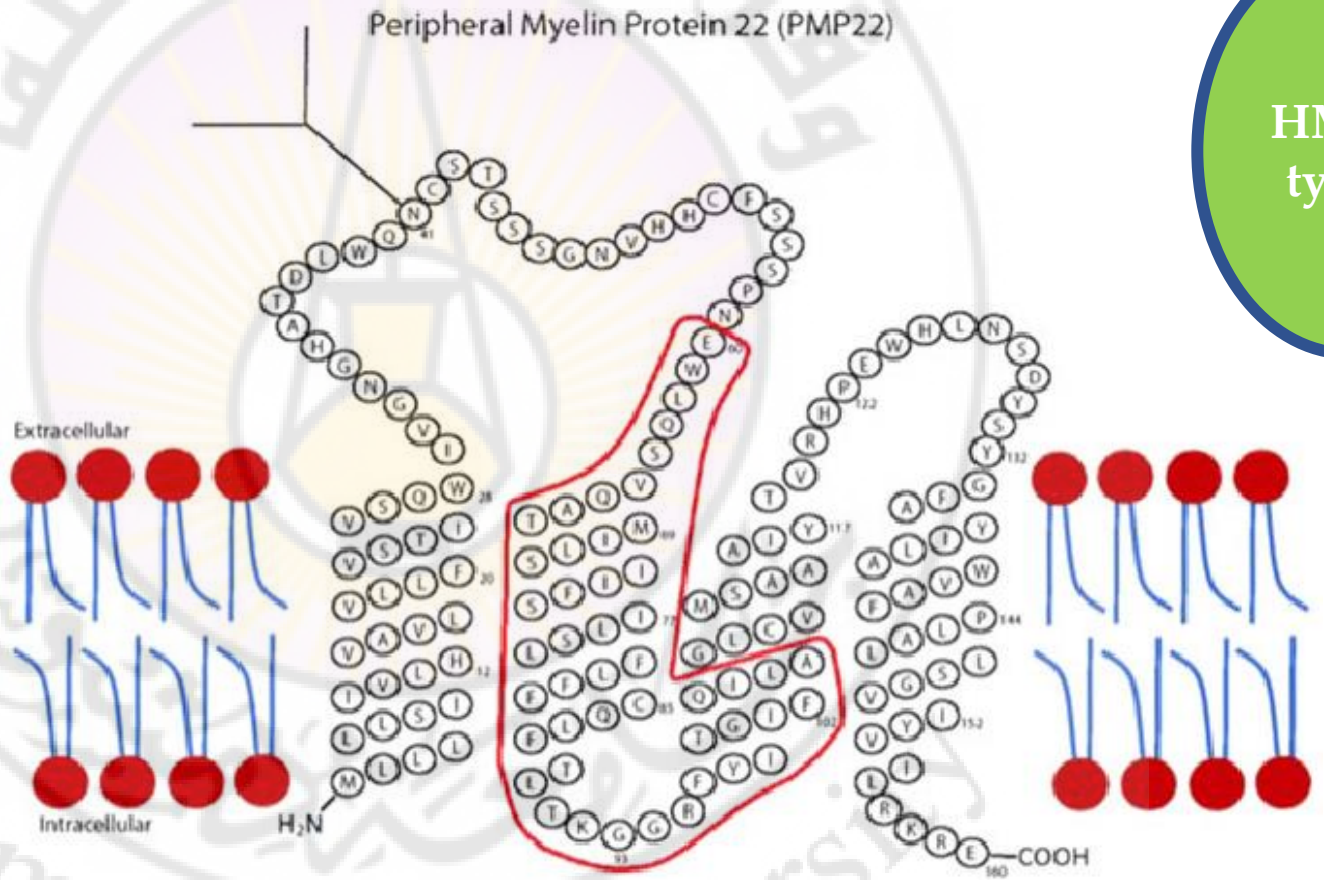
Peripheral neuropathy



Thickened greater auricular nerve,

Peripheral neuropathy

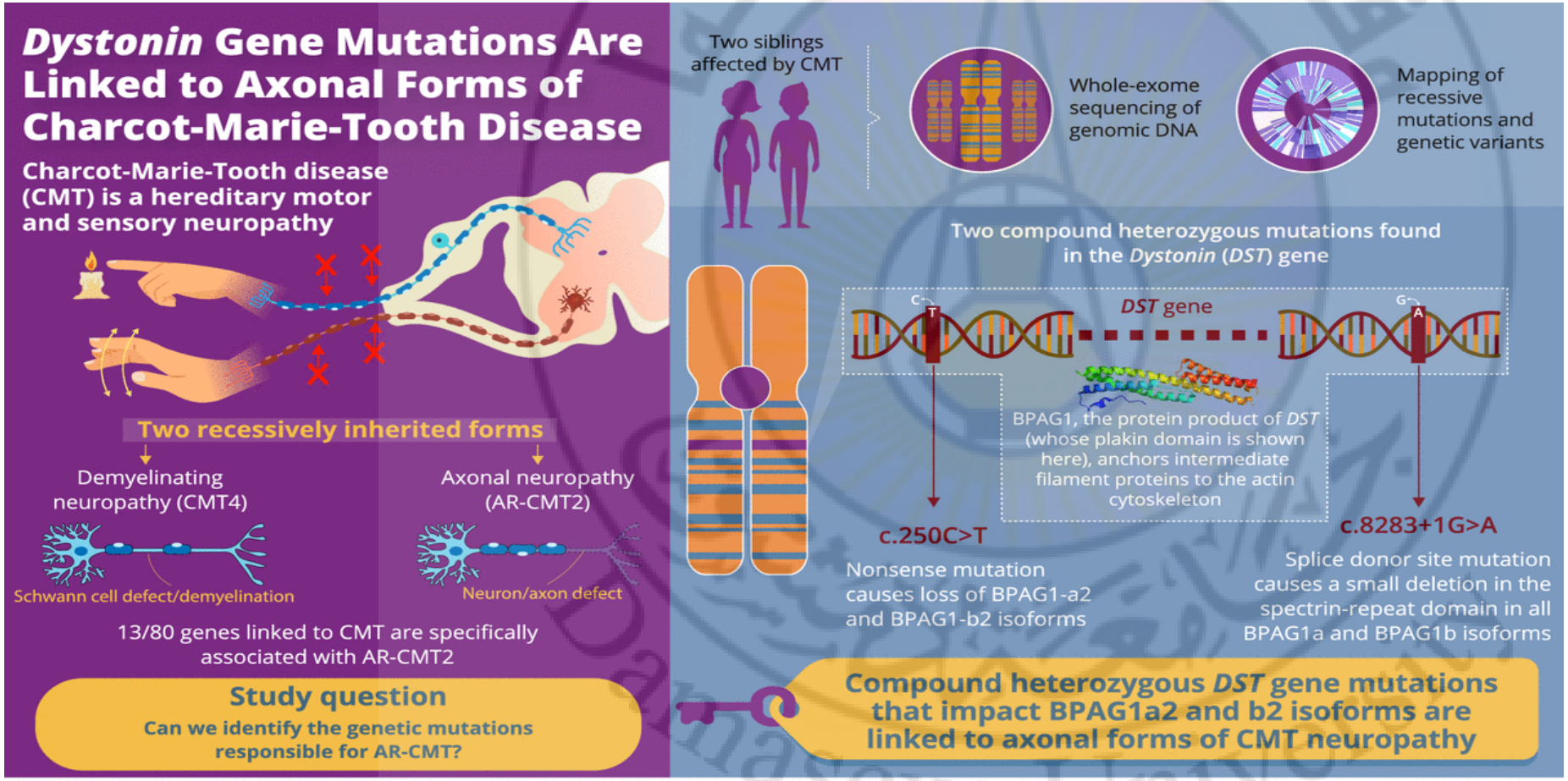




HMSN type I

Duplication in the gene for peripheral myelin protein 22

Peripheral neuropathy



doi:10.1212/NXG.0000000000000496

Neurology®

HMSN type II

زوجان ماتوا من ٧٠٠٠ سنه

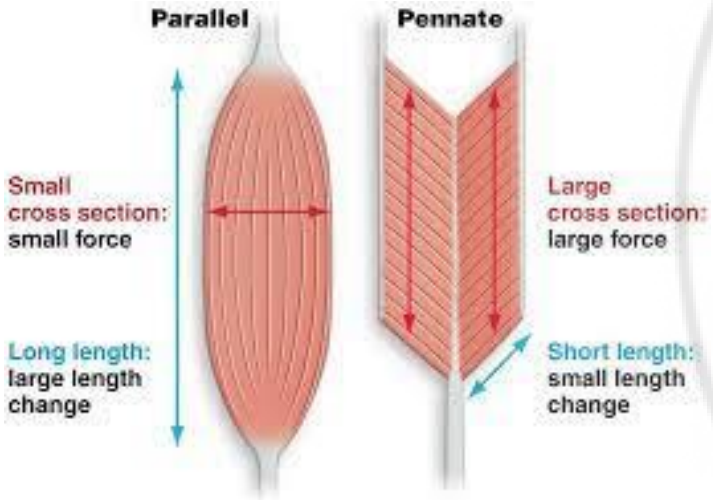
Muscle disease

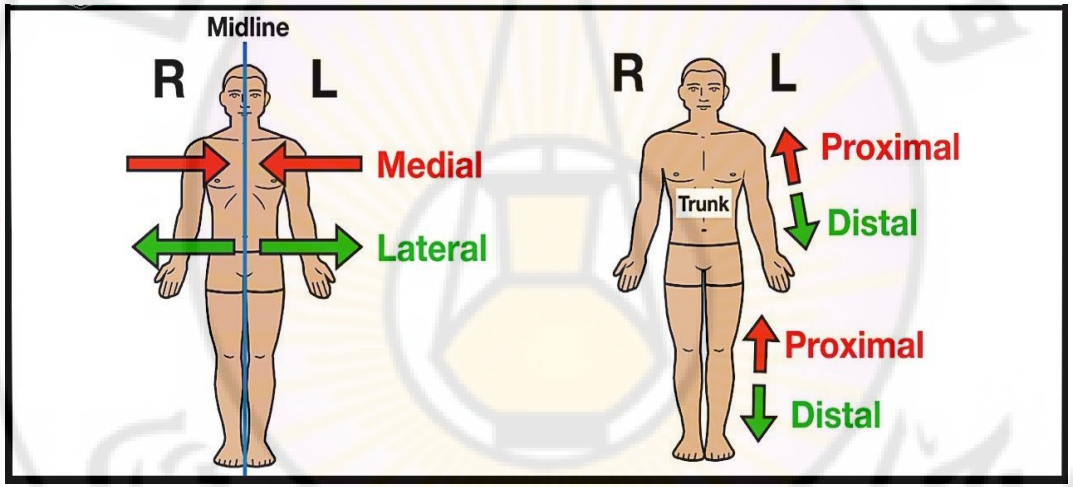
DEF: The term *dystrophy means abnormal growth.*

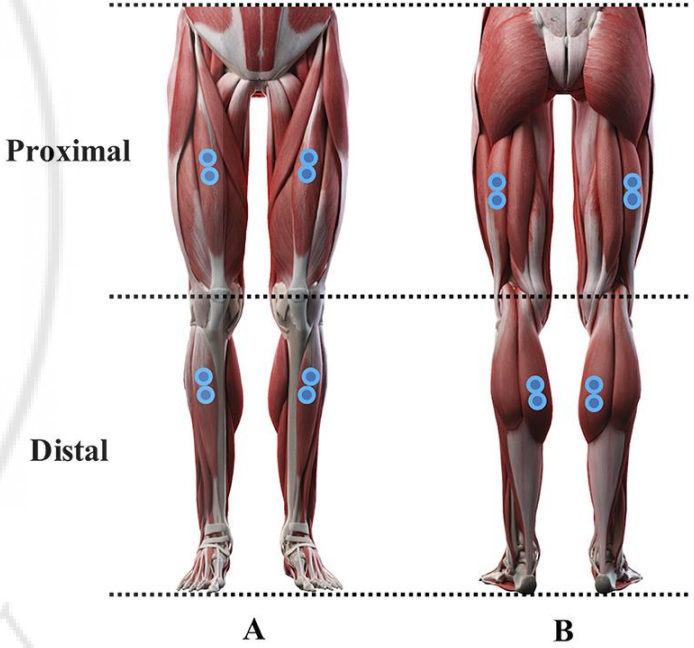
Muscular dystrophy is distinguished from all other neuromuscular diseases by 4 obligatory criteria:

- It is a Primary myopathy
- It has a genetic basis,
- The course is progressive, and
- Degeneration and death of muscle fibers occur at some stage in the disease.

Muscle disease







The proximal compartment has the structure of a parallel muscle, whereas the distal compartment is considered a pennate muscle because it has a pennate angle

Muscle disease

Table 1. Aetiological classification of muscle diseases

Acquired muscle diseases	Inflammatory myopathies	Dermatomyositis
		Myositis associated with connective tissue disease
		Polymyositis
		Necrotizing autoimmune myopathy
		Inclusion body myositis
	Toxic myopathies	
	Endocrine myopathies	
	Infective myopathies	
	Amyloid myopathy	
Genetic muscle diseases	Muscular dystrophies and congenital myopathies	The dystrophinopathies: Duchenne and Becker
		Myotonic dystrophy 1 and 2
		Facioscapulohumeral muscular dystrophy
		Limb girdle muscular dystrophy
		Myofibrillar myopathies
		Distal myopathies
		Oculopharyngeal muscular dystrophy
	Metabolic/inborn error of metabolism	Mitochondrial disease
		Glycogen metabolism disorders
		Fatty acid oxidation disorders
	Muscle channelopathies	

Muscle disease

Inherited

1 Muscular dystrophies, whose genetic basis is increasingly understood in terms of gene and gene product identification.

Duchenne	X-linked recessive gene
Myotonic dystrophy	Autosomal dominant gene
Facio-scapulo-humeral	Autosomal dominant gene
Limb girdle	Not a single entity (variable inheritance)

2 Muscle diseases in which an inherited biochemical defect is present.

Specific enzyme deficiencies occur which disrupt the pathways of carbohydrate or fat oxidation, often with accumulation of substrate within the muscle cell. The enzyme deficiency may be within the muscle cell cytoplasm, interfering with the utilization of glycogen or glucose, or it may be within the mitochondria of muscle cells (and cells of other organs) blocking the metabolism of pyruvate, fatty acids or individual elements of Krebs cycle.

In other diseases of this sort, there is uncoupling of the electrical excitation of muscle fibres and their contraction. This is the case in McArdle's syndrome, and in malignant hyperpyrexia where sustained muscle contraction may occur in the absence of nerve stimulation.

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Muscle disease

Acquired

1 Immunologically mediated inflammatory disease, e.g.
- *polymyositis*
- *dermatomyositis*

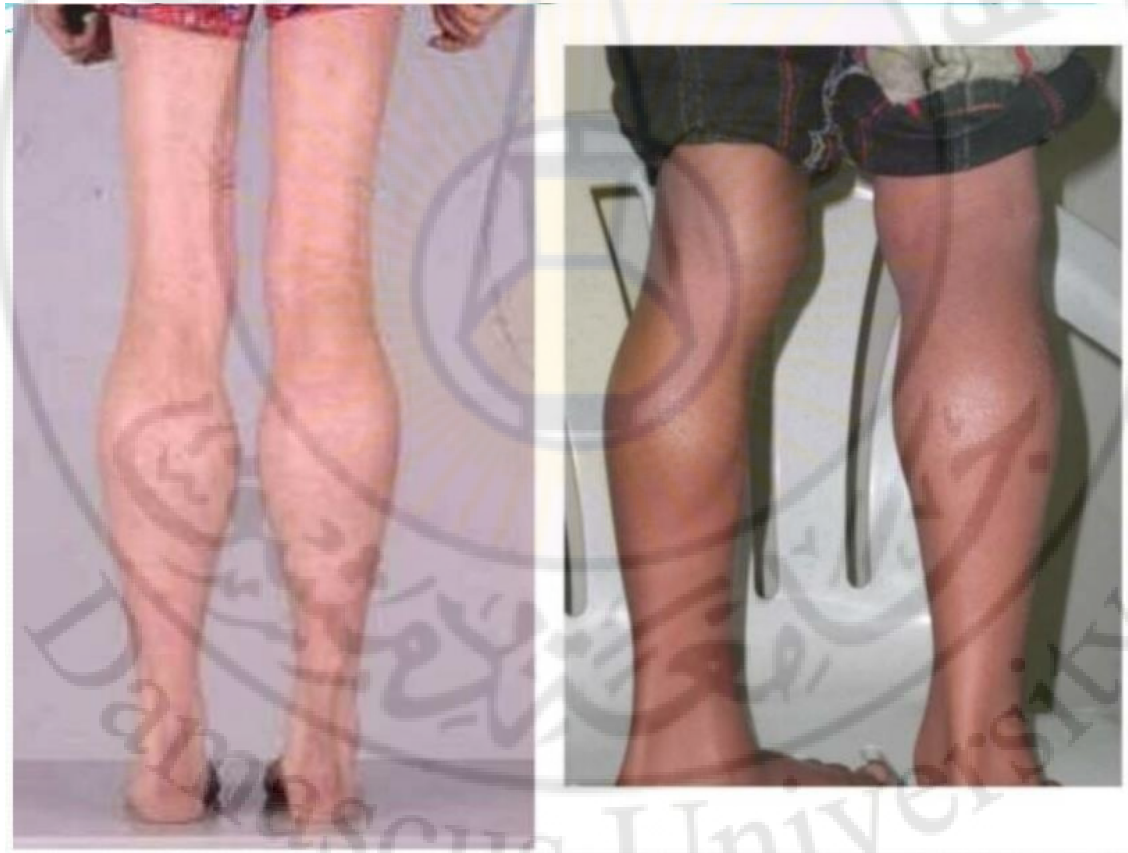
2 Non-inflammatory myopathy, e.g.
- *corticosteroids*
- *thyrotoxicosis*

Muscle disease

Key features of Duchenne muscular dystrophy

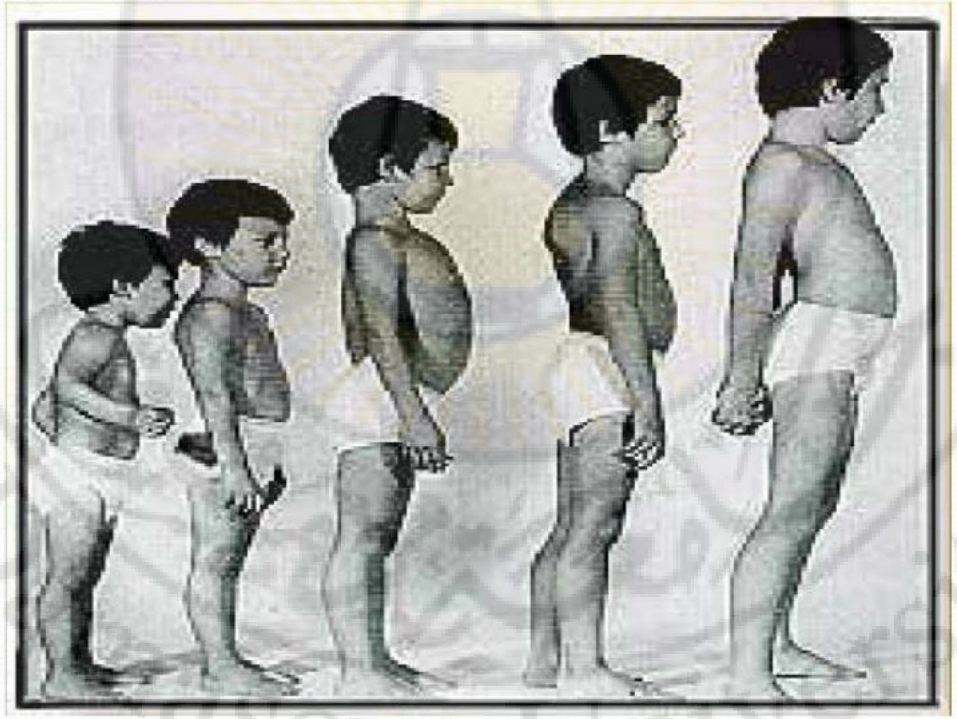
- Young
- Male
- Generalized weakness
- Muscle wasting
- Calf pseudohypertrophy
- Gower's sign

Muscle disease



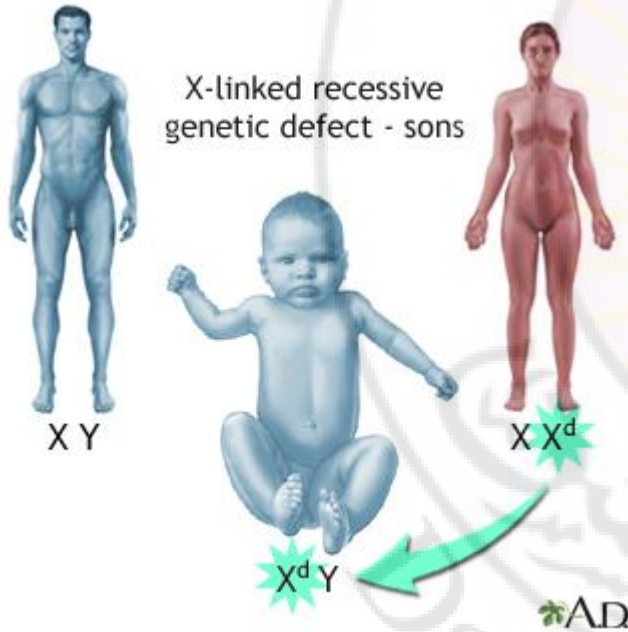
Muscle disease

Posture changes during progression of DMD



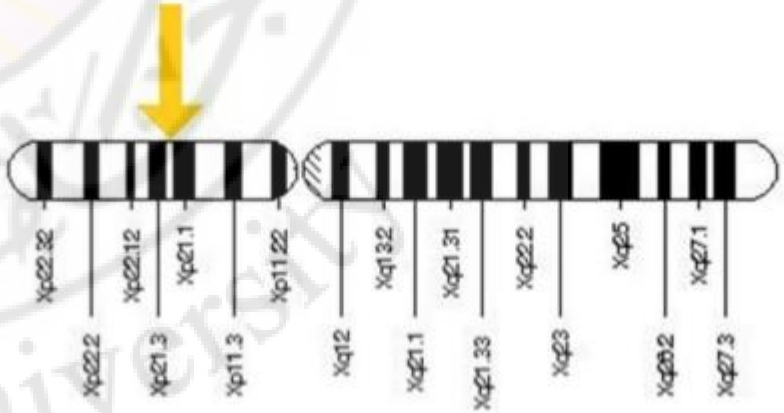
Muscle disease

Muscle disease



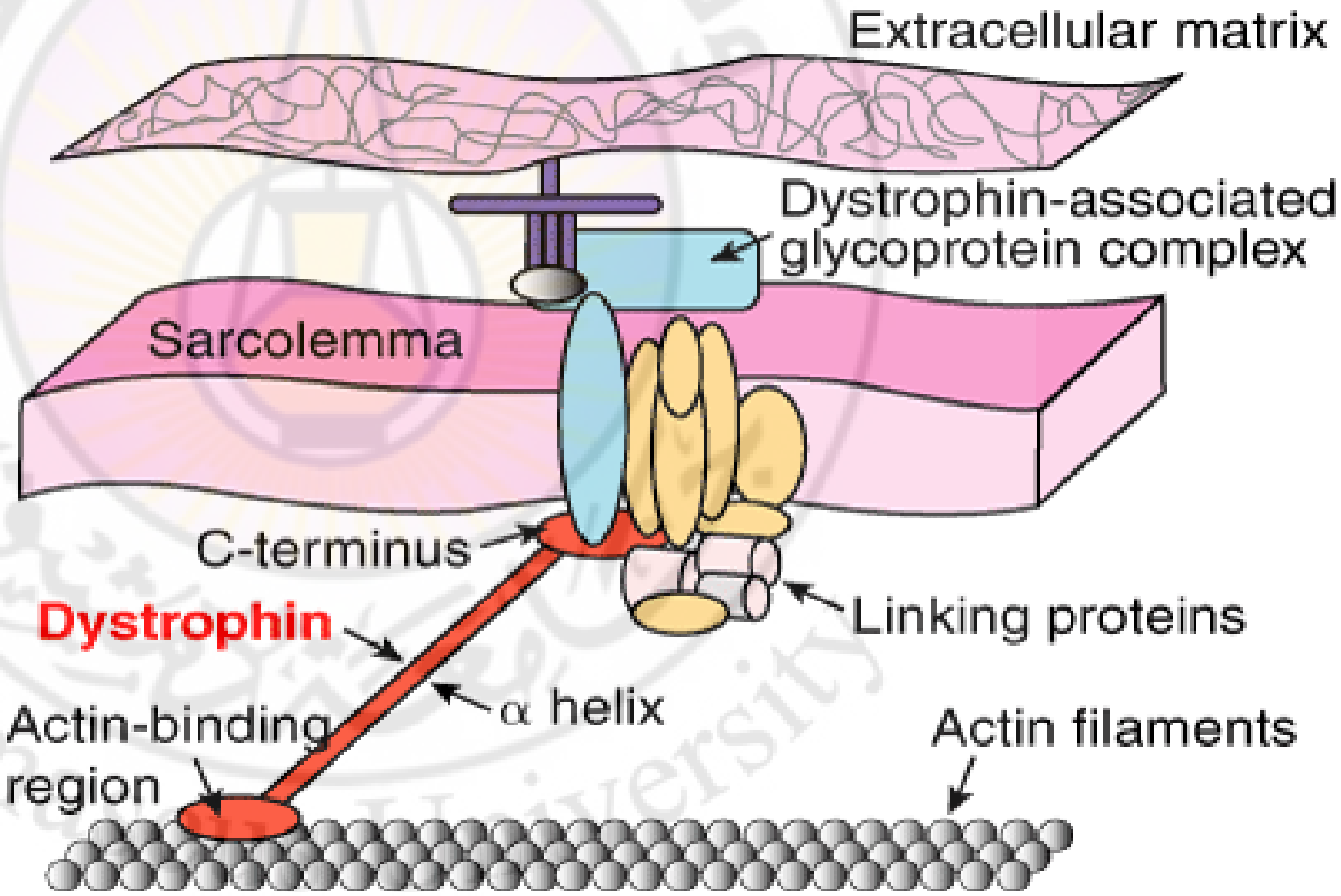
Dystrophin Gene

- The largest known human gene (vulnerable to mutation)
- Provides instructions for making a protein called ***Dystrophin.***
- **LOCATION:**
  - (i) Short (p) arm of the X chromosome at position 21.2. (Xp21.2)
  - (ii) Primarily in muscles used for movement (skeletal muscles) and in heart (cardiac) muscle. Small amounts of dystrophin are present in nerve cells in the brain.

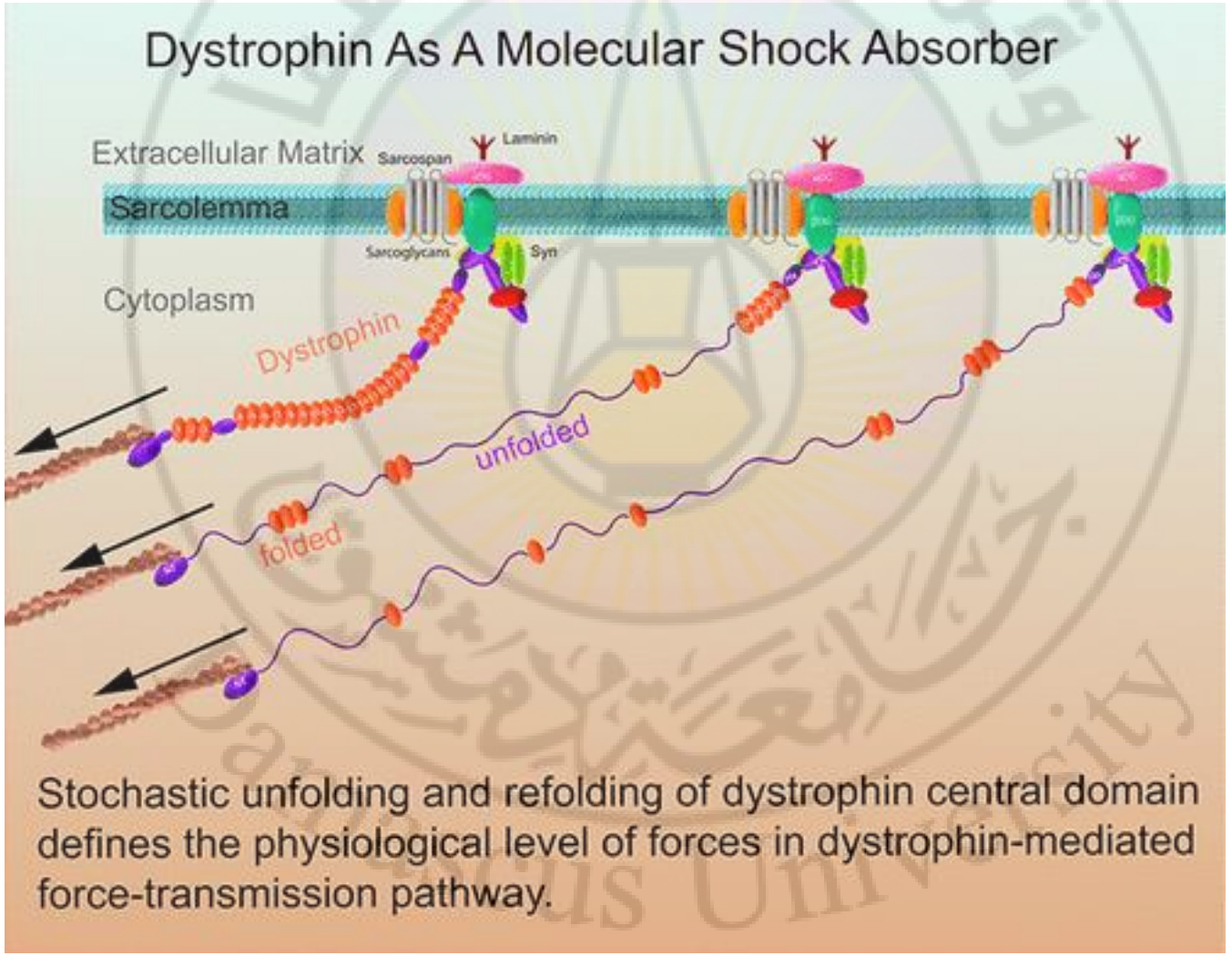


Muscle disease

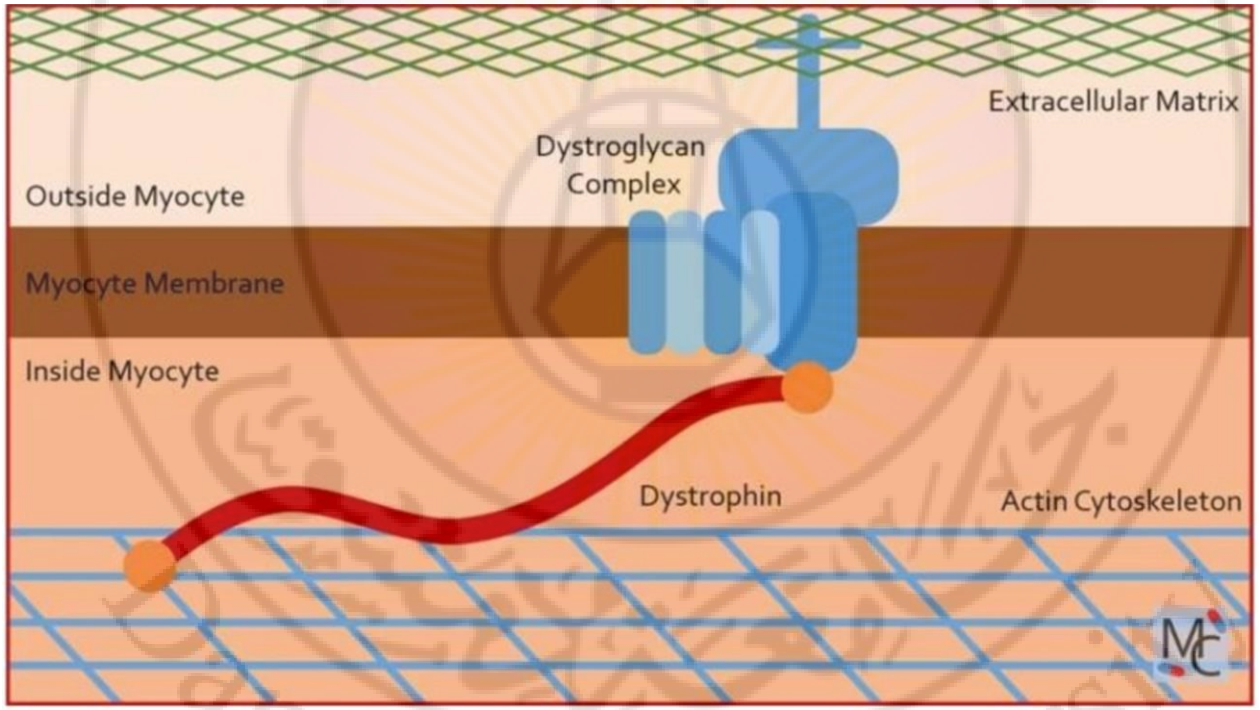
Dystrophin is a rod-shaped cytoplasmic protein, and a vital part of a protein complex that connects the cytoskeleton of a muscle fiber to the surrounding extracellular matrix through the cell membrane. This complex is variously known as the costamere or the dystrophin-associated protein complex (DAPC).



Muscle disease

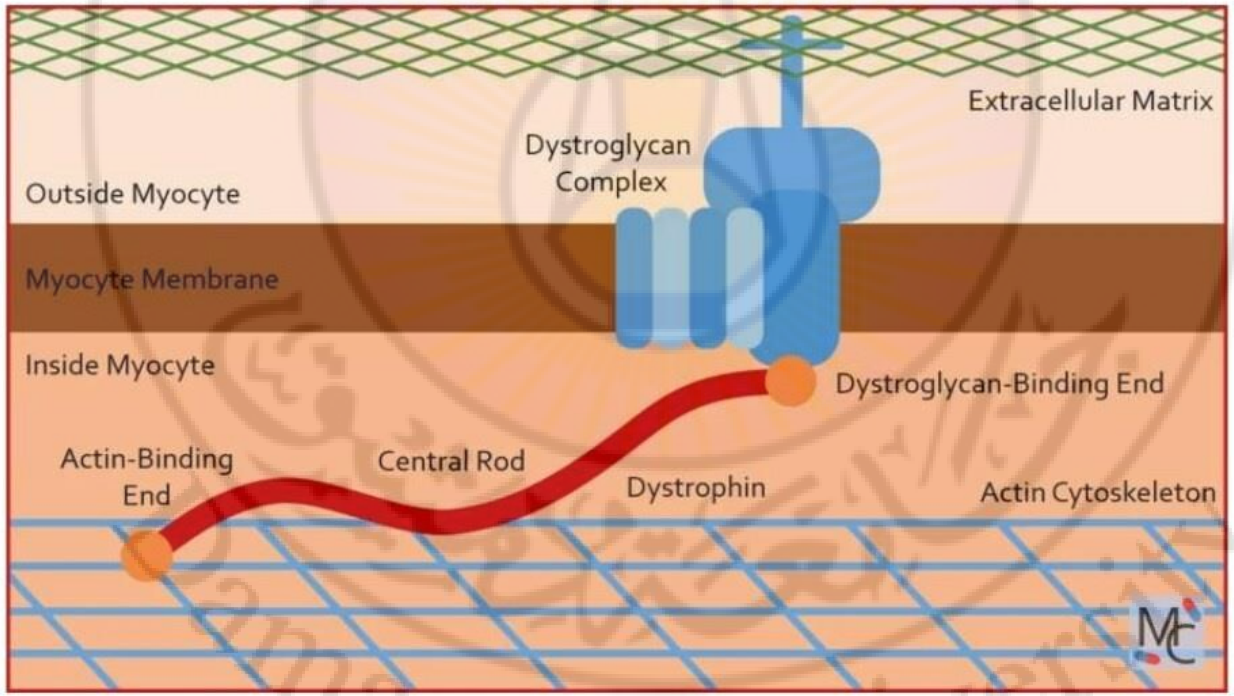


Muscle disease



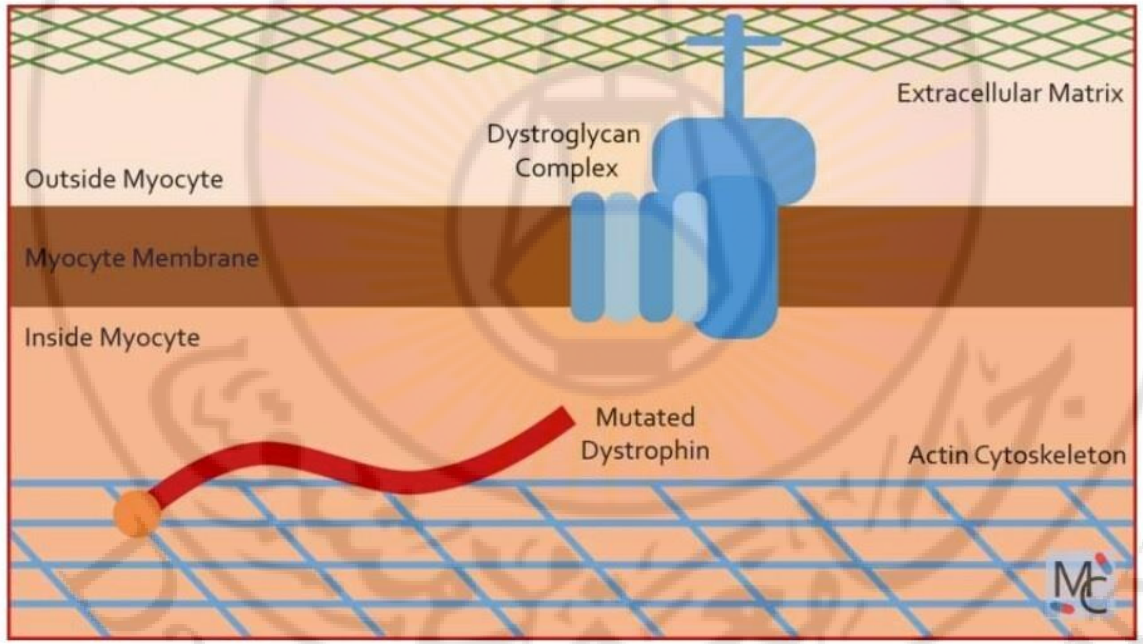
Muscle disease

Normal protein



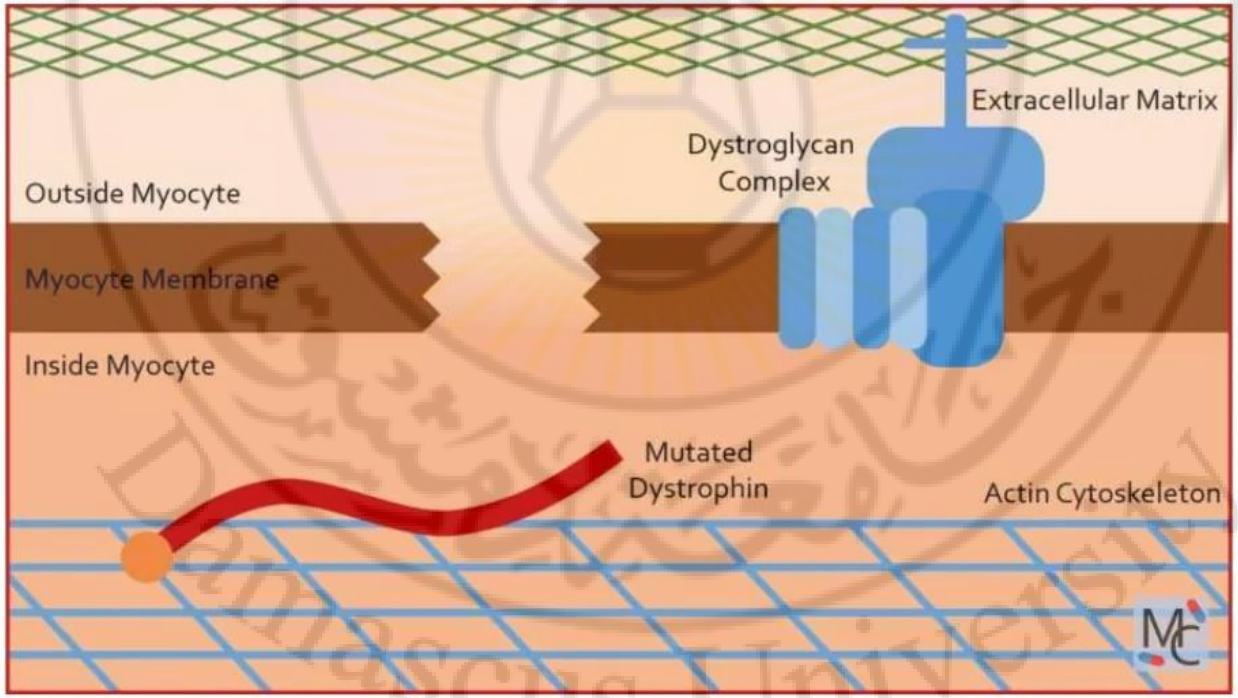
Muscle disease

Mutation

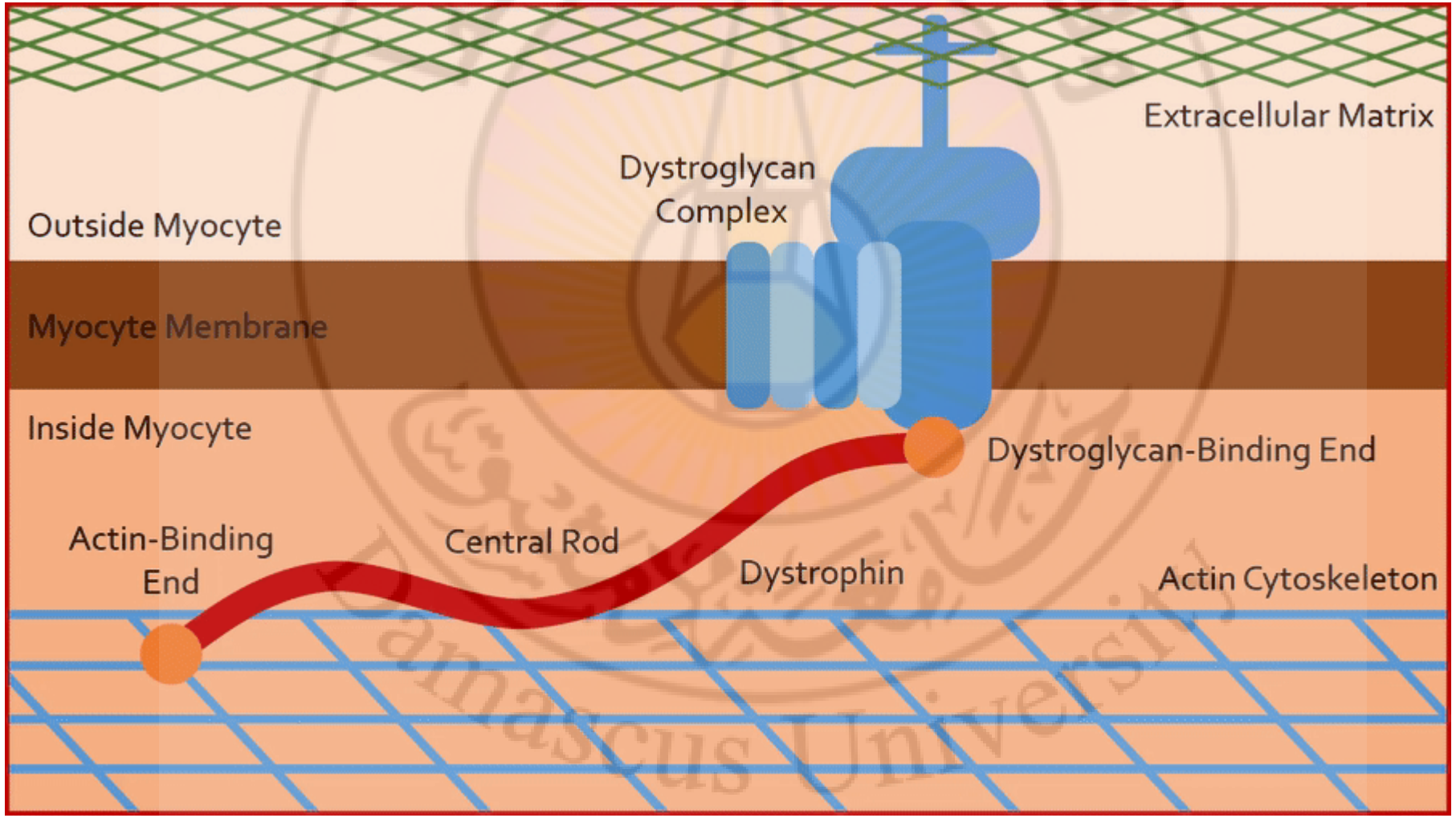


Muscle disease

Breakage in cell membrane following muscle contractions

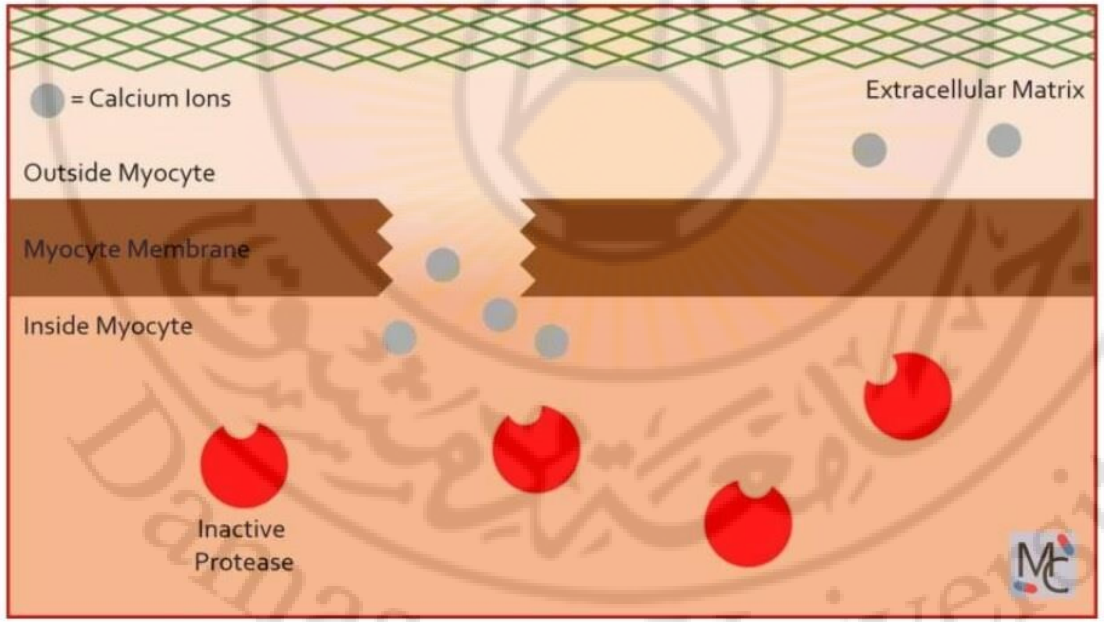


Muscle disease



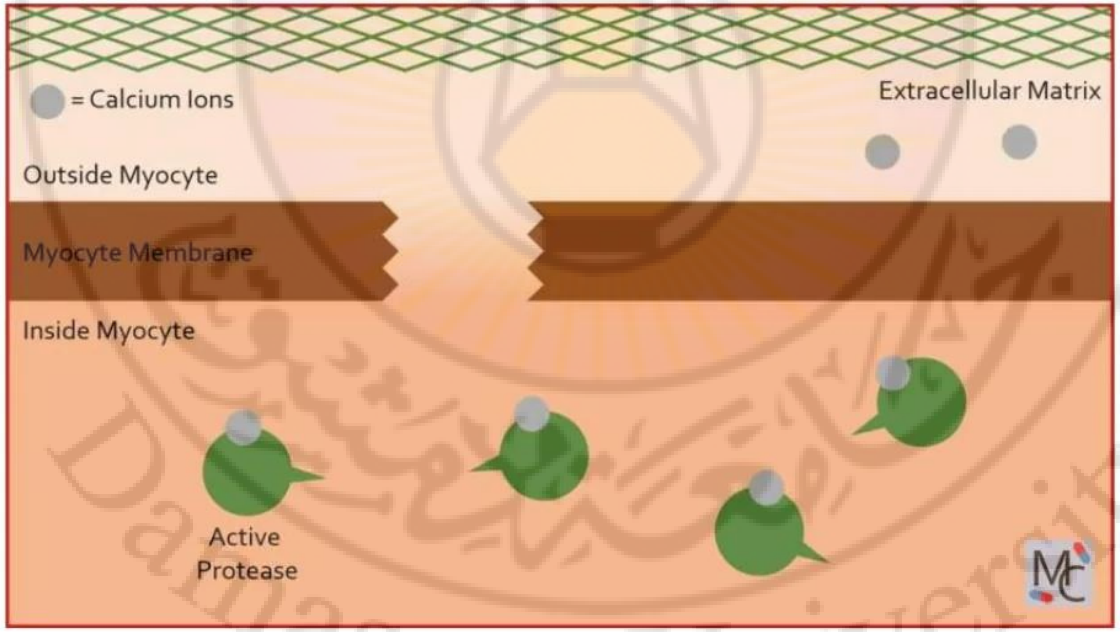
Muscle disease

Entry/leakage of calcium
from ECF to ICF



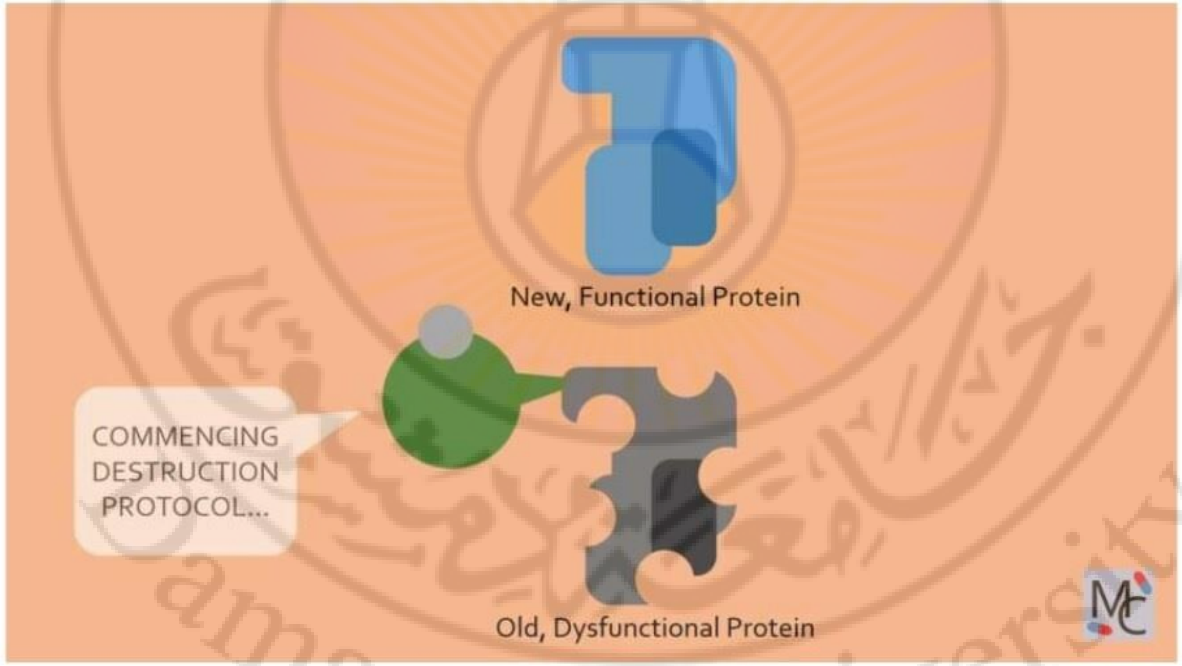
Muscle disease

Calcium activates proteases that breakdown proteins in the muscle



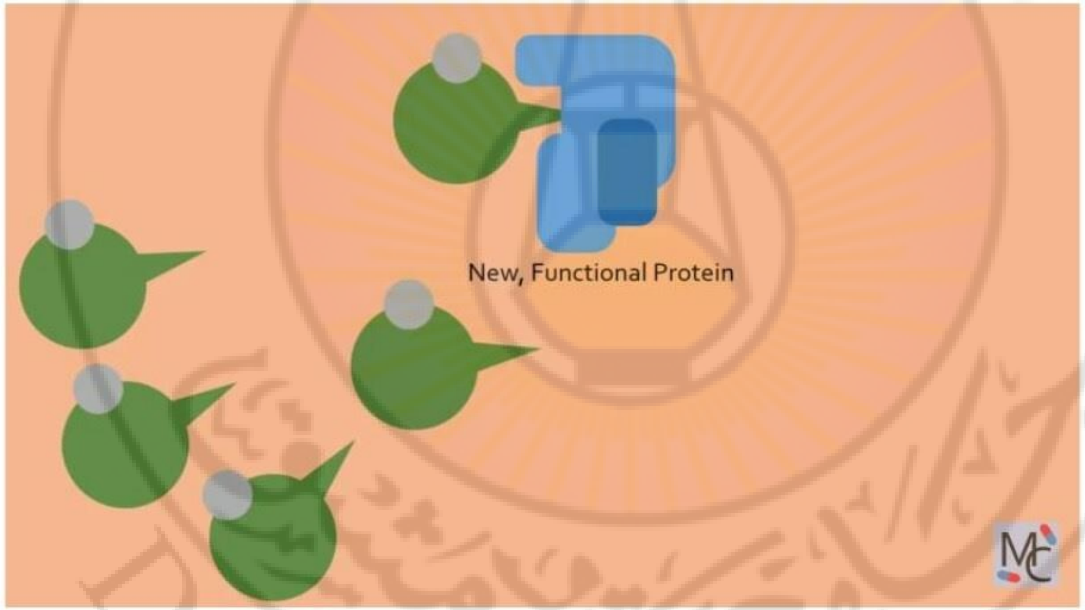
Muscle disease

Action of proteases in normal levels



Muscle disease

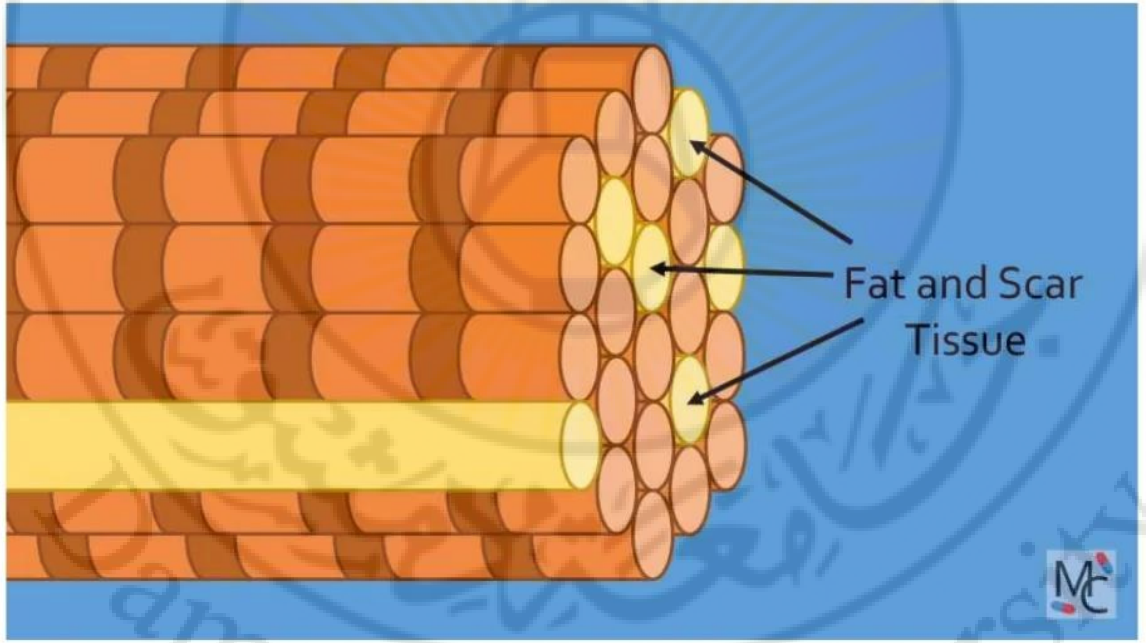
When protease conc inc



Muscle disease

Leakage of CK – inc CK

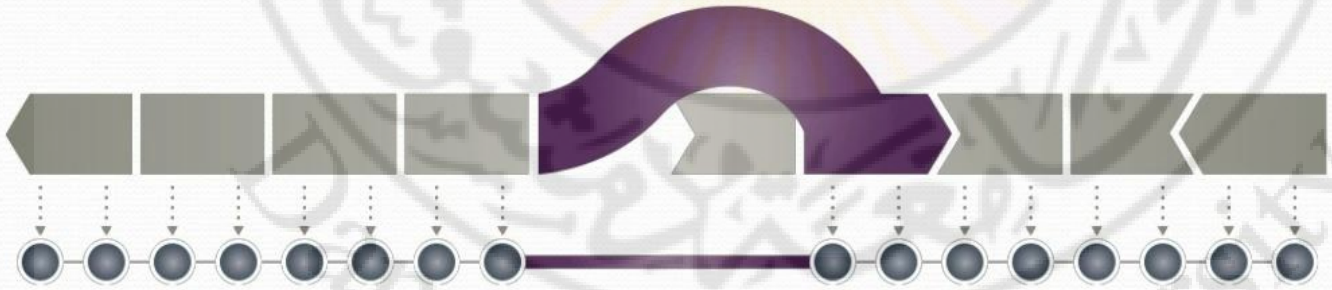
Muscle disease



Muscle disease

EXON SKIPPING

In DMD, exon skipping is a potential treatment approach that is under investigation to correct for specific genetic mutations and restore production of dystrophin protein.



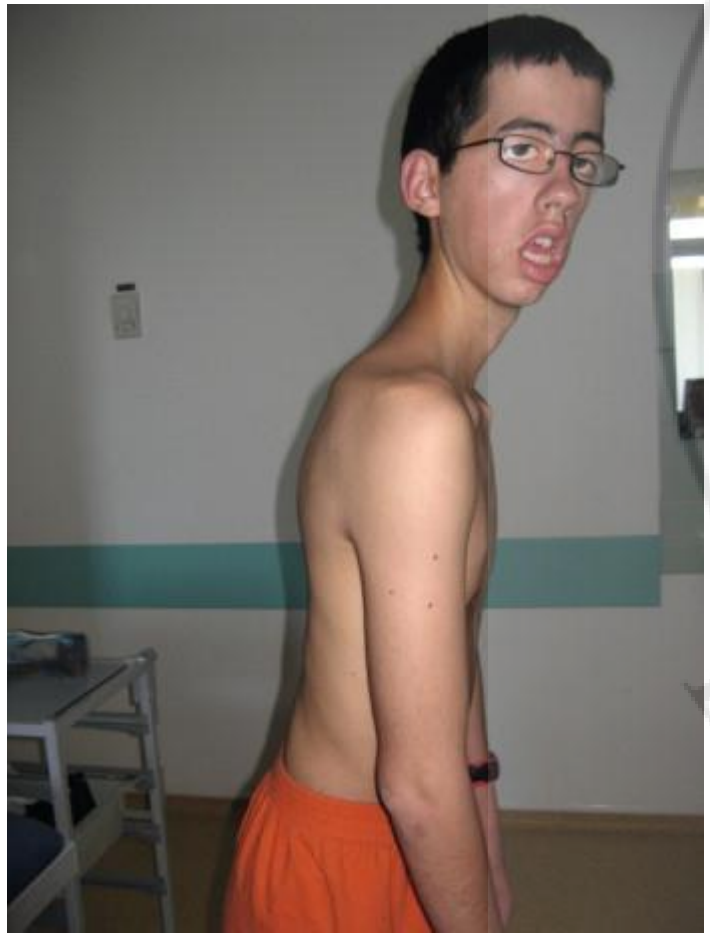
Muscle disease

- As the name suggests, the principle of exon skipping is to encourage the cellular machinery to 'skip over' an exon. Small pieces of DNA called antisense oligonucleotides (AOs) or 'molecular patches' are used to mask the exon that you want to skip, so that it is ignored during protein production

Muscle disease

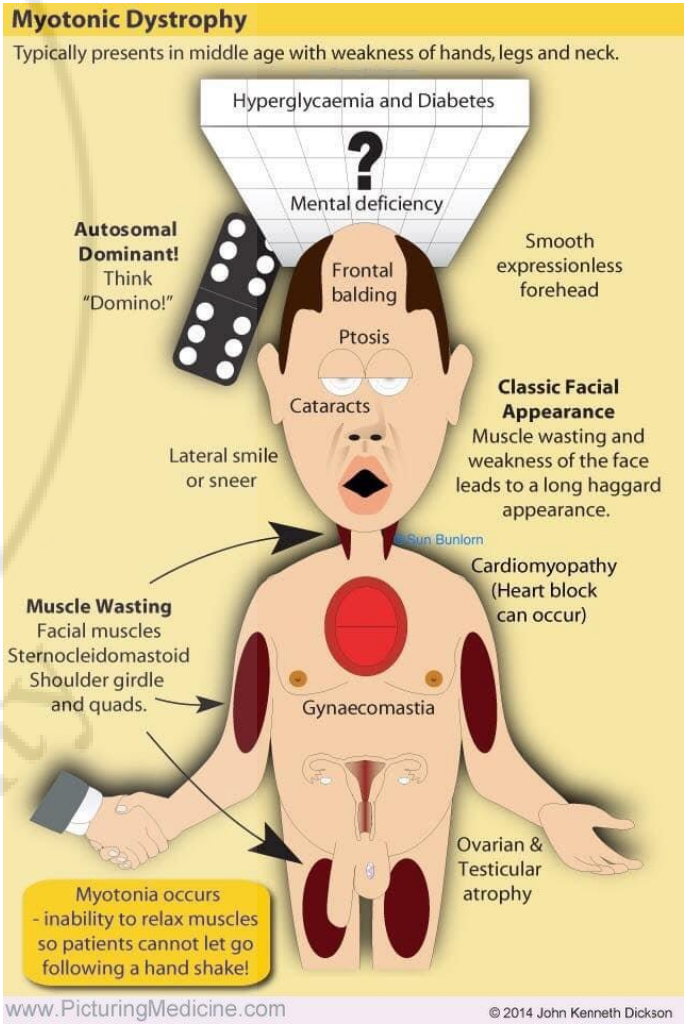
Drisapersen and eteplirsen are exon 51 skipping antisense oligonucleotides that bind RNA and skip (bridge) over the defective exon, thus producing a shorter but potentially functional dystrophin protein.

Muscle disease



Key features of myotonic dystrophy

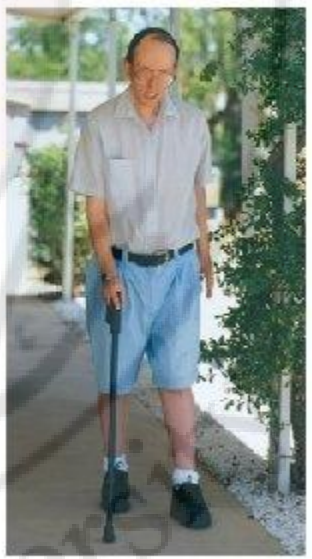
- Either sex
- Glum-looking from facial weakness and ptosis
- Frontal balding
- Glasses or previous cataract surgery
- Hand muscles show wasting and myotonia



Muscle disease

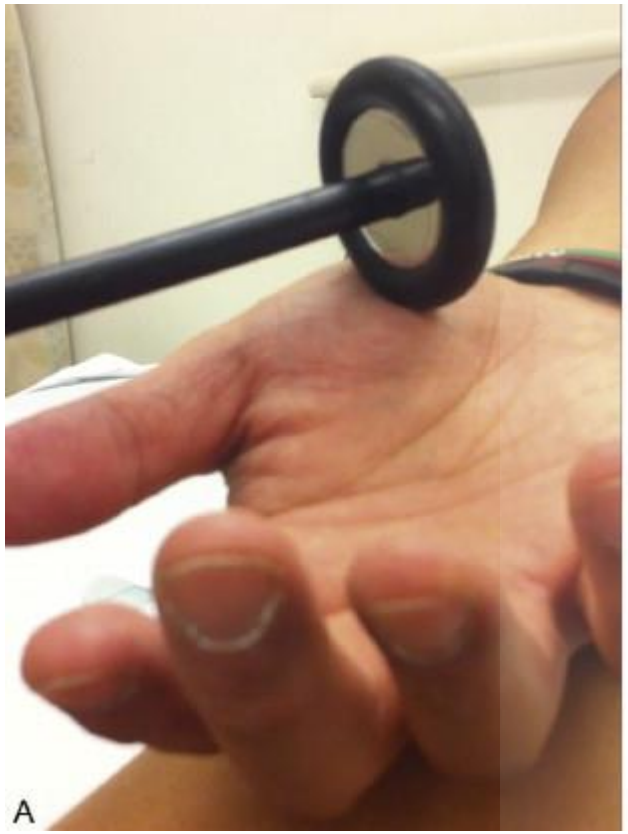
Myotonic Dystrophy Type 1

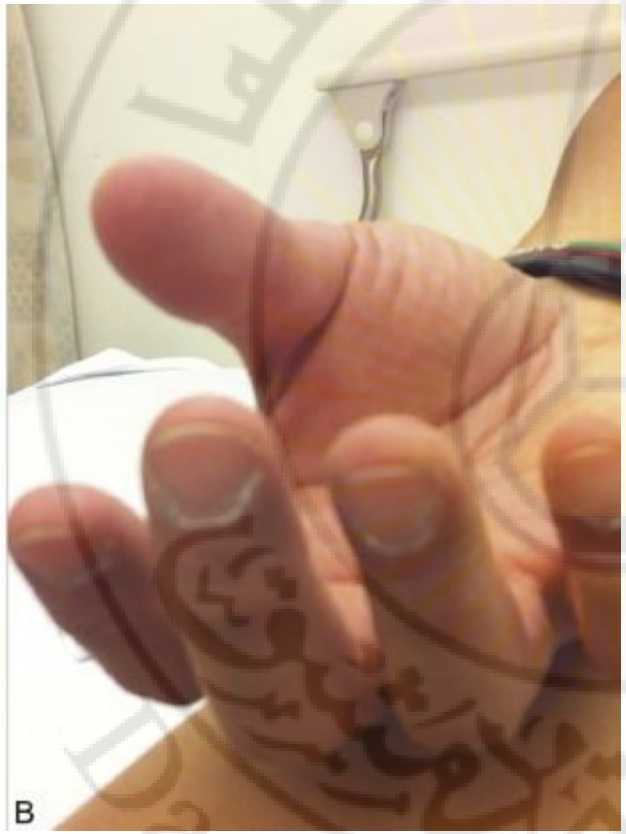
Tapered limbs



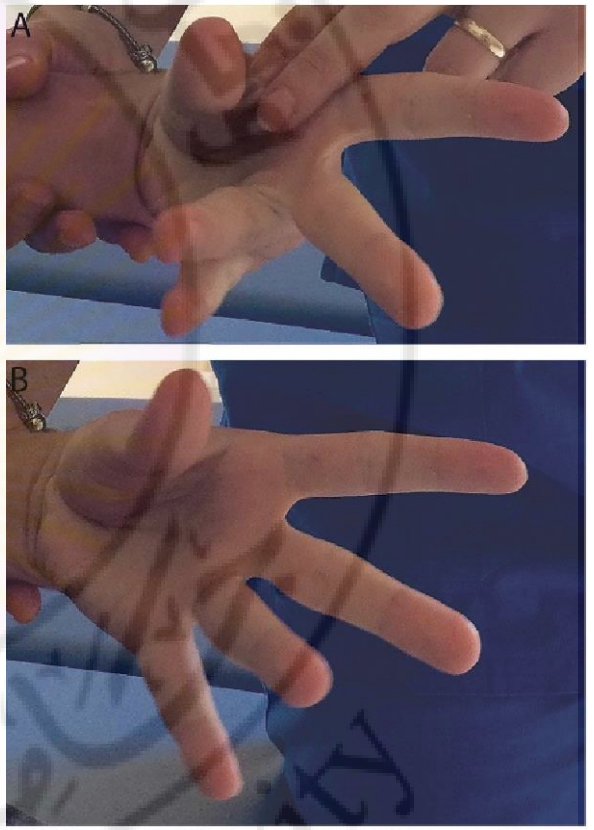
Long thin face

Muscle disease



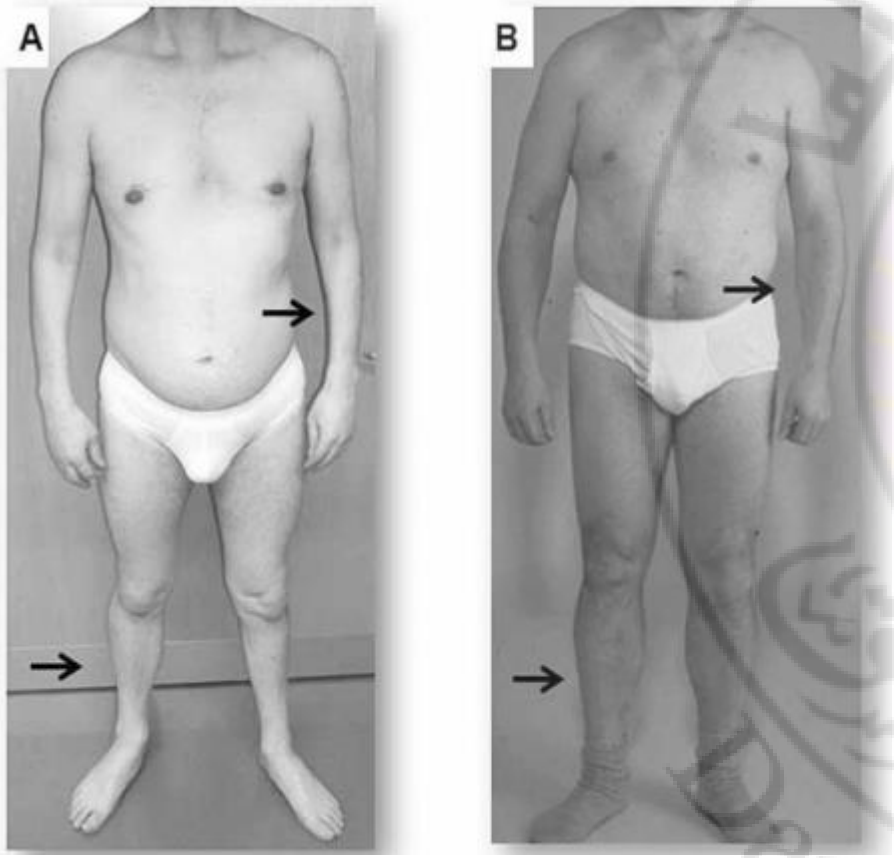


Percussion Myotonia



Grip Myotonia

Muscle disease



DM1 specific
at the beginning

- prominent distal weakness
- distal muscle atrophy
- gastrointestinal problems
- reduced life expectancy
- onset 0-50 yrs

congenital DM1

- retardation
- hypotonia
- facial diplegia
- «tent»-mouth

DM core pattern

- myotonia
- muscle weaknes and atrophy
- early cataract
- cardiac arrhythmias
- dilatative cardiomyopathy
- cognitive dysfuncion
- hypersomnia
- hyper-GGt
- insulin resistance
- testicular atrophy
- frontal balding
- hypogammaglobulinemia
- muscle pain

DM2 specific
at the beginning

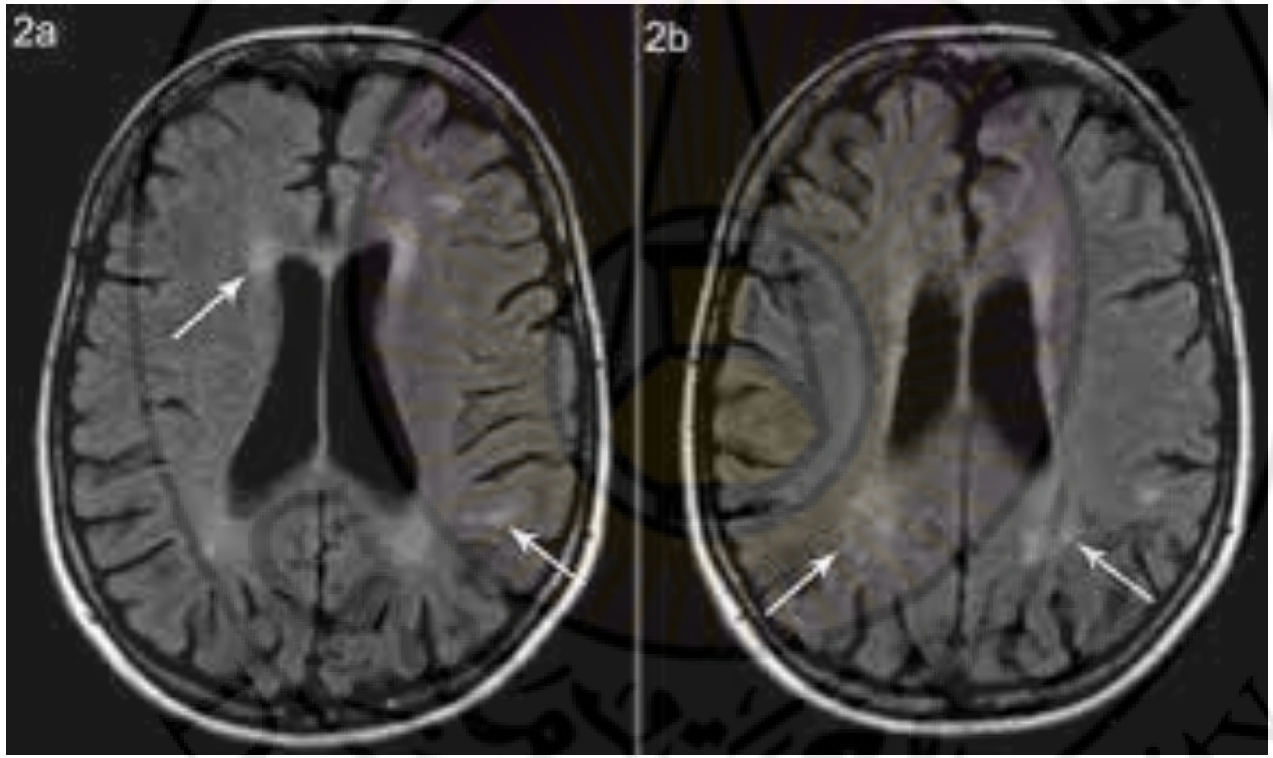
- prominent proximal weakness
- proximal muscle atrophy
- calf hypertrophy
- tremor
- onset >15 yrs; mean >40 yrs

Differences in clinical presentation of adult DM1 and DM2. A classic forearm atrophy is shown for patient with DM1 (A) but not with DM2 (B). The "core" characteristic of DM2 is a typical predominant lower leg weakness and atrophy (B)

Muscle disease

Items	DM1	DM2
Chromosomal locus	19q 13.3	3q 21.3
Gene	*DMPK*	*ZNF9*
Inheritance	Autosomal dominant	Autosomal dominant
Mechanism	CTG repeat expansion	CCTG repeat expansion
Normal repeat size	Up to 37	Up to 27
Pathologic repeat size	>50 CTG	>75 CCTG?
Expanded repeat range	50-4,000	75-5,000->11000 CCTG
Anticipation	Yes	— (?)

Muscle disease



Myotonic dystrophy type 1

Muscle disease

Facio-scapulo-humeral dystrophy

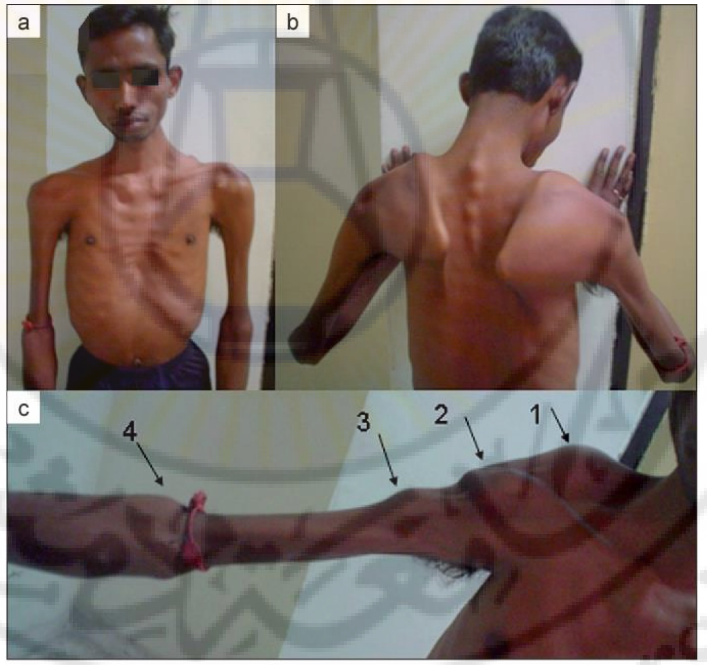
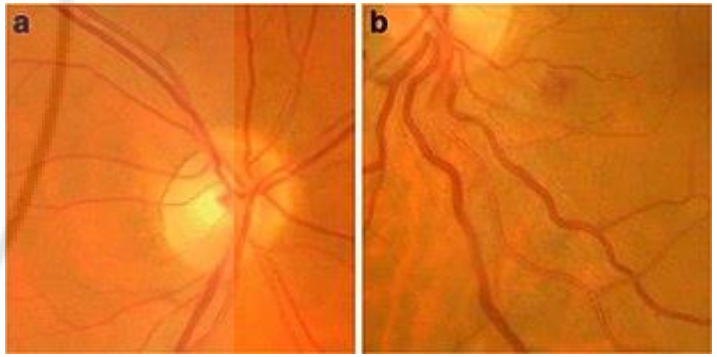


Figure 2: Clinical signs in facio-scapulo-humeral dystrophy: (a) Facial

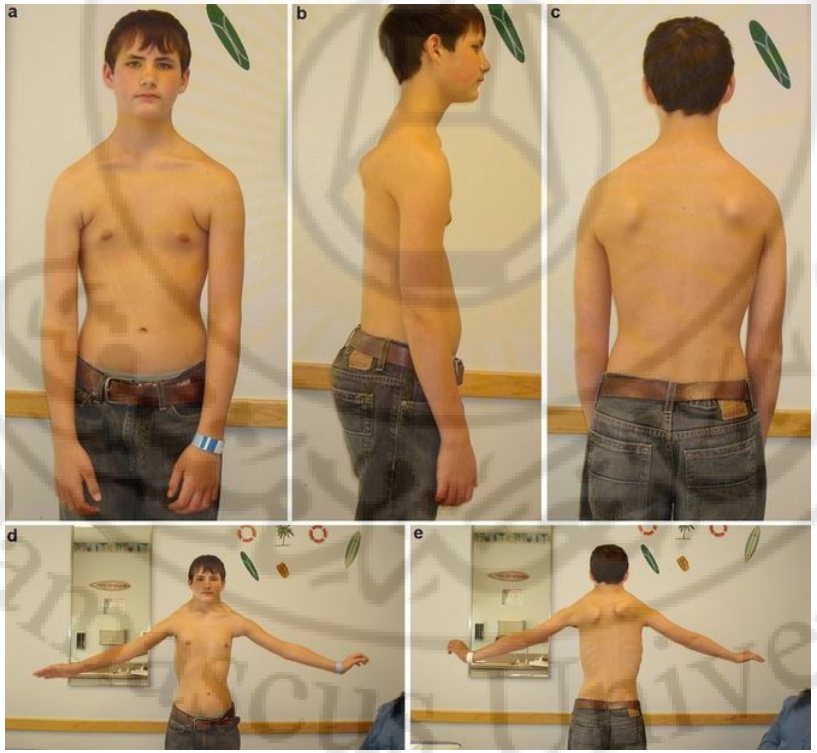


Funduscopy of the retinal: (A) normal blood vessels (B) tortuous blood vessels, as often seen with FSHD

Wasting and weakness of the facial, scapular and humeral muscles

Muscle disease

Facio-scapulo-humeral dystrophy



Muscle disease

Facio-scapulo-humeral dystrophy

The *DUX4* gene is the focal point of FSHD genetics. Normally, *DUX4* is expressed during embryogenesis and later repressed in all tissues except the testes. In FSHD, there is failure of *DUX4* repression and continued production of DUX4 protein, which is toxic to muscles. The mechanism of failed *DUX4* repression is hypomethylation of *DUX4* and its surrounding DNA on the tip of chromosome 4 (4q35), allowing transcription of *DUX4* into messenger RNA (mRNA)

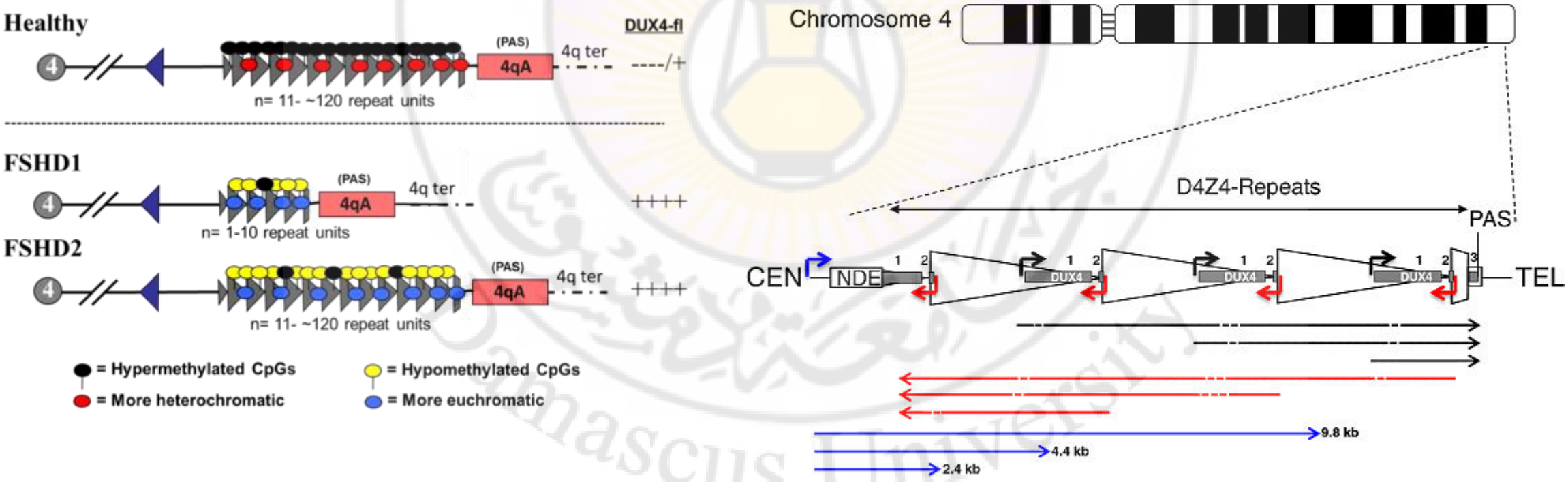
IN SUMMARY:

Shortened D4Z4 + 4qA + hypomethylation of D4Z4 = FSHD Type 1
chromosome 4

SMCHD1 mutation + 4qA + hypomethylation of D4Z4 = FSHD Type 2
chromosome 18 **chromosome 4**

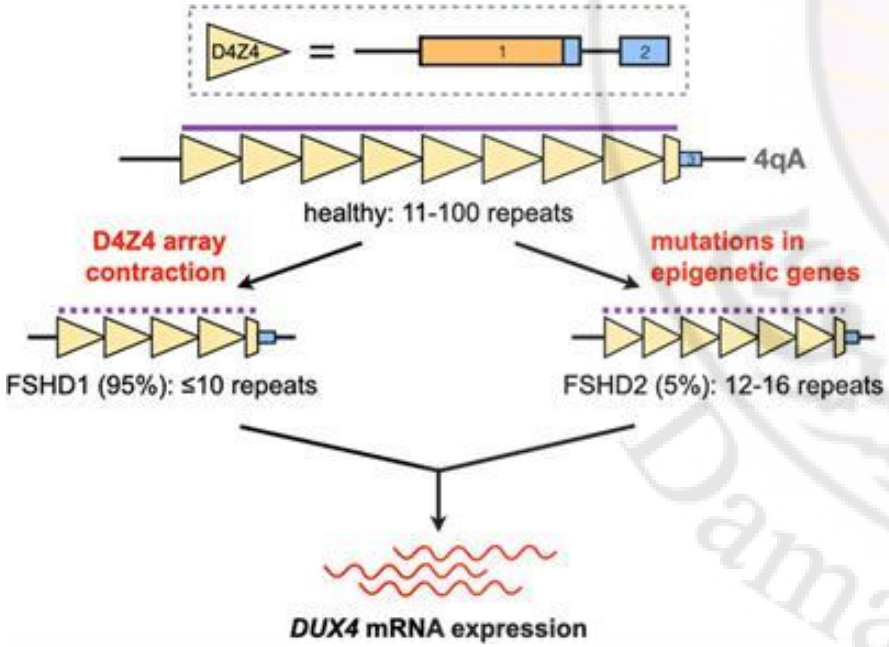
Muscle disease

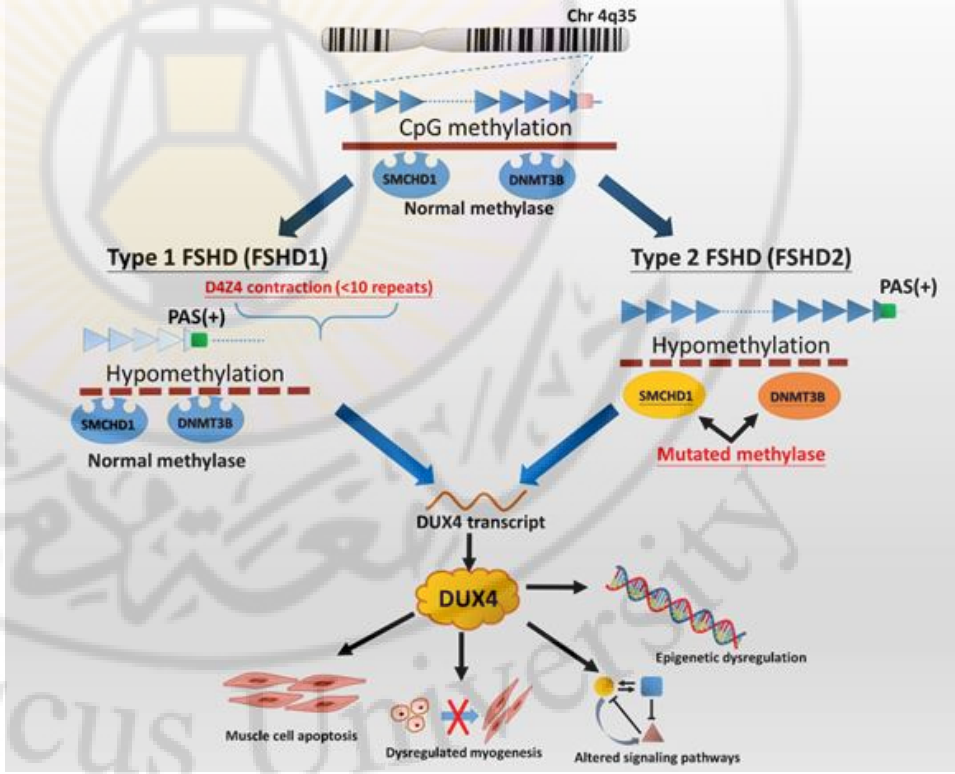
Facio-scapulo-humeral dystrophy



Muscle disease

Facio-scapulo-humeral dystrophy





Muscle disease

Limb girdle weakness:

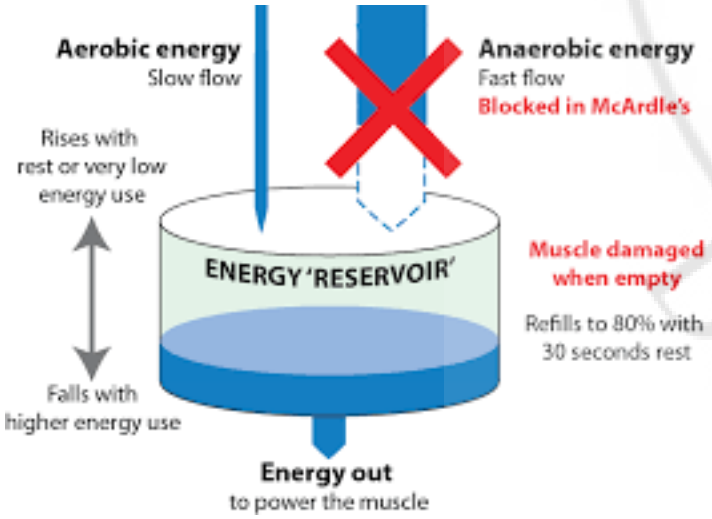
- polymyositis
- myopathy associated with endocrine disease
- metabolic myopathies
- drug-induced myopathies, e.g. steroids
- limb girdle dystrophy

Muscle disease

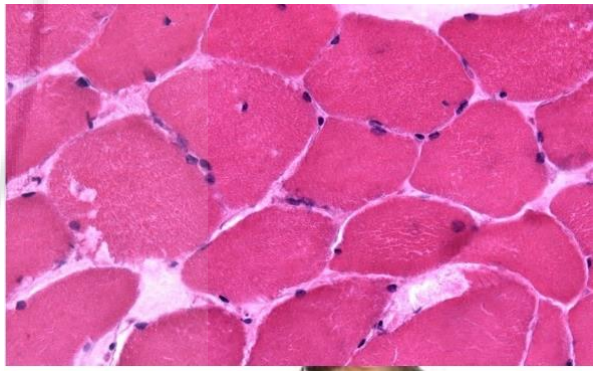
Conditions caused by inherited biochemical defects

McARDLE'S DISEASE

- Increased muscle glycogen, but can't break it down! Severe muscle cramps (decreased ATP), myoglobinuria.
- Skeletal Muscle glycogen phosphorylase



The onset of this disease is usually noticed in childhood, but often not diagnosed until the third or fourth decade of life. Symptoms include exercise intolerance with muscle pain, early fatigue, painful cramps, and myoglobin in the urine (often provoked by a bout of exercise)



Muscle disease

Conditions caused by inherited biochemical defects

Symptoms do not occur until an affected family member has a general anaesthetic, particularly if halothane or suxamethonium chloride is used

Mutations in the *RYR1* gene

↓

Altered Ca^{2+} release channel protein (RYR1) (eg, substitution of Cys for Arg^{615})

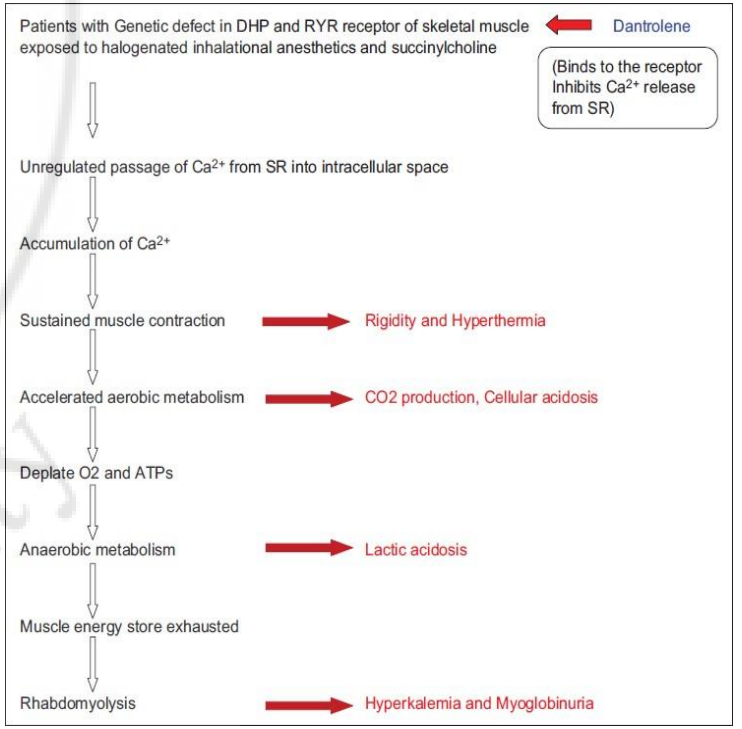
↓

Mutated channel opens more easily and stays open longer, thus flooding the cytosol with Ca^{2+}

↓

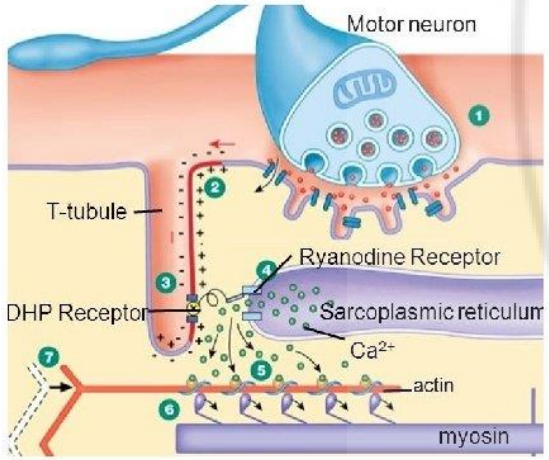
High intracellular levels of Ca^{2+} stimulate sustained muscle contraction (rigidity); high Ca^{2+} also stimulates breakdown of glycogen, glycolysis, and aerobic metabolism (resulting in excessive production of heat)

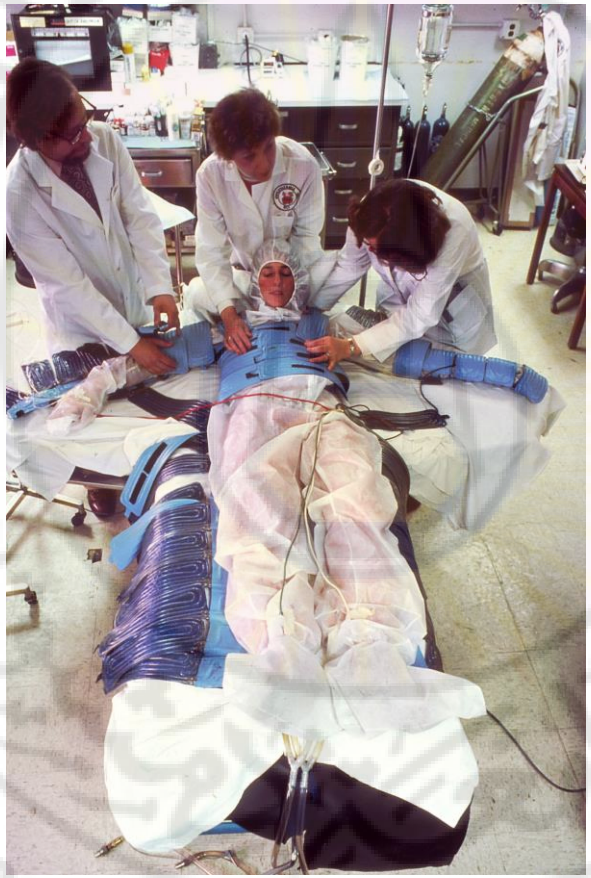
Malignant hyperpyrexia

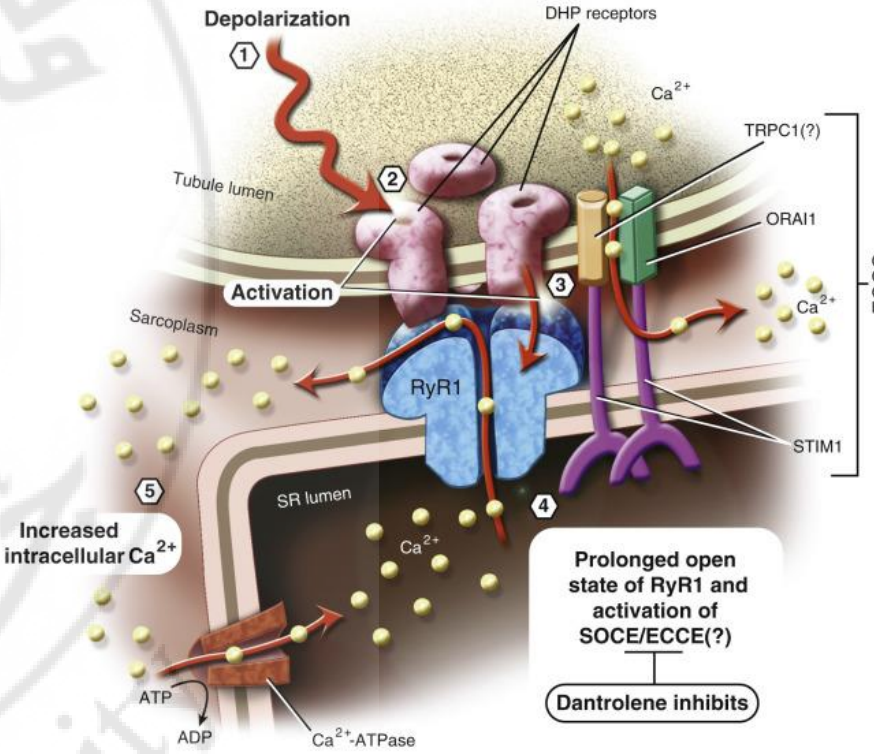


Muscle disease

Dantrolene







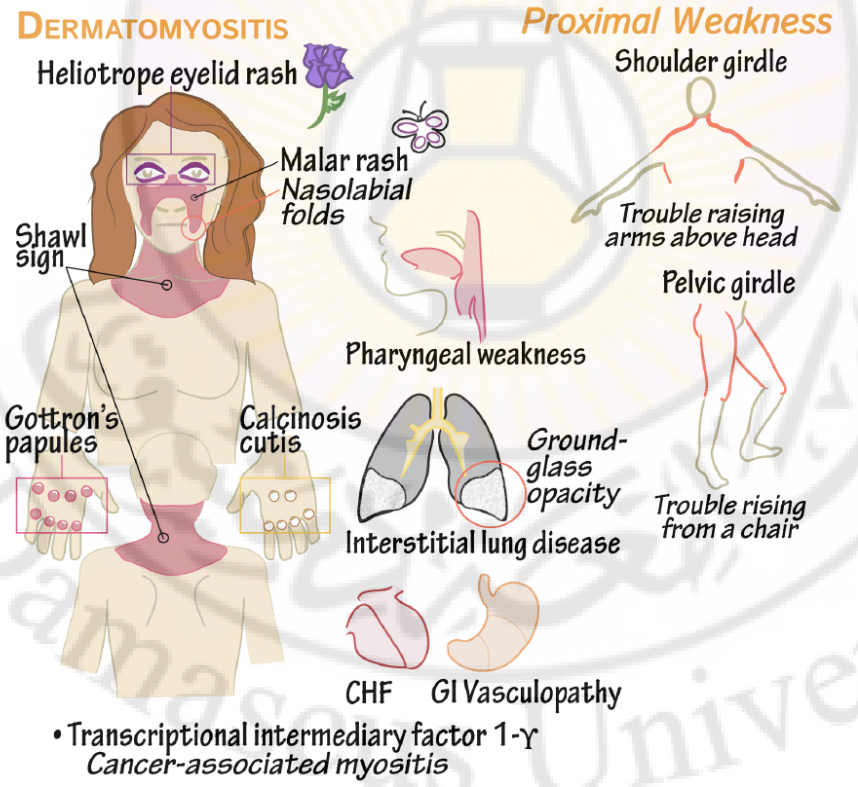
Malignant hyperpyrexia

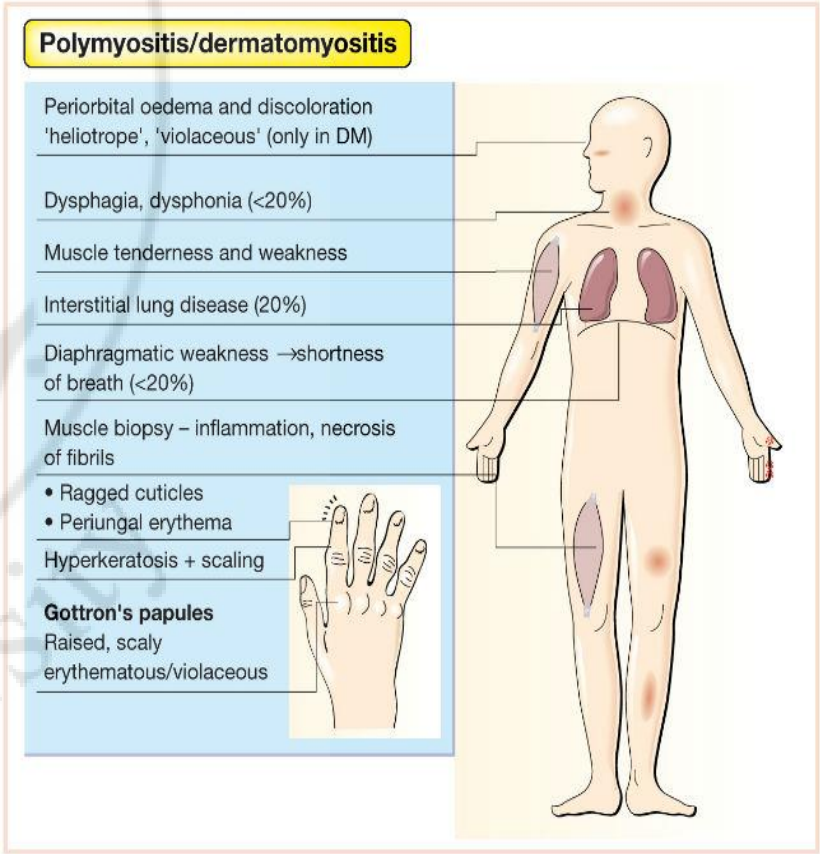
Muscle disease

Polymyositis and dermatomyositis

Clinical features of dermatomyositis	
Muscle weakness	• Proximal, symmetric • Weakness in UE = LE
Skin findings	• Gottron's papules • Heliotrope rash
Extramuscular findings	• Interstitial lung disease • Dysphagia • Myocarditis
Diagnosis	• ↑ CPK, aldolase, LDH • Anti-RNP,anti-Jo-1, anti-Mi2 • Diagnostic uncertainty o EMG o Biopsy (skin/muscle)
Management	• High-dose glucocorticoids **PLUS** glucocorticoid-sparing agent • Screening for malignancy

CPK = creatinine phosphokinase; EMG = electromyography; LDH = lactate dehydrogenase; LE = lower extremity; UE = upper extremity.





Muscle disease

Polymyositis and dermatomyositis

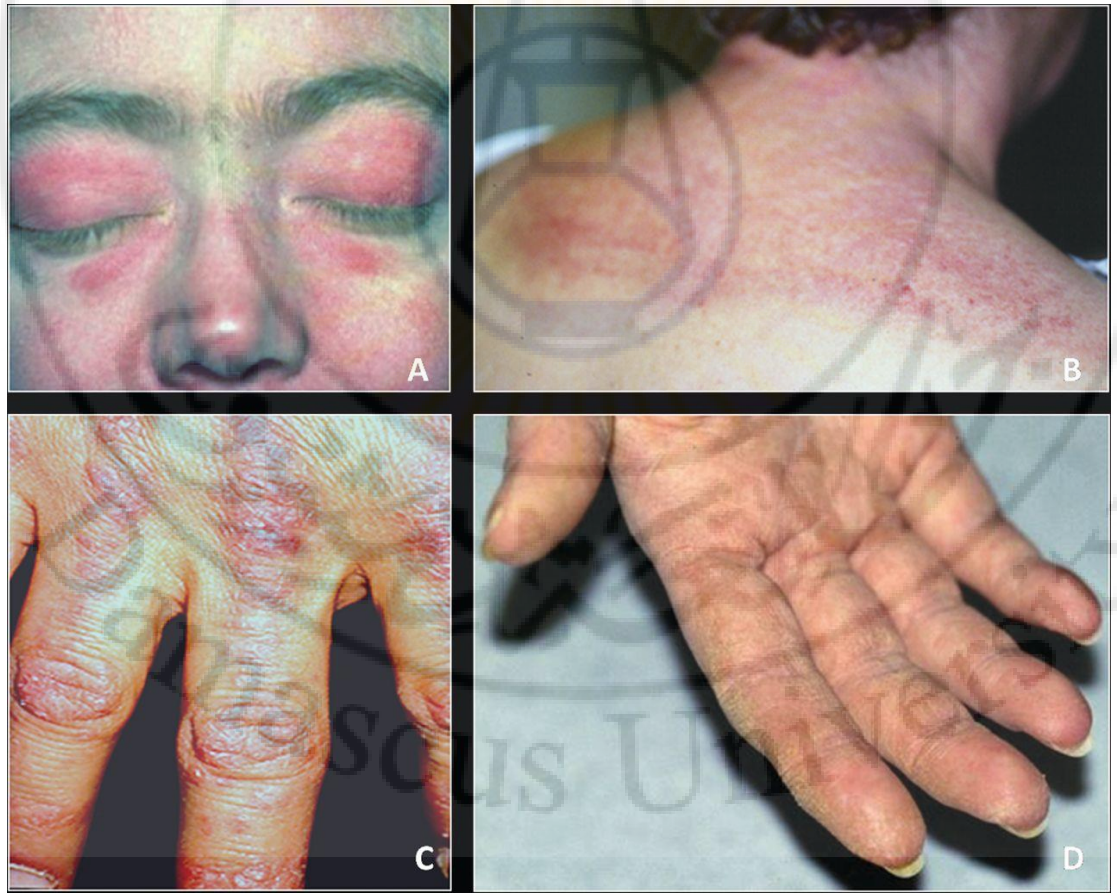
What is polymyositis (PM)?

Polymyositis is one of the inflammatory myopathies, a group of muscle diseases that involves inflammation of the muscles or associated tissues, such as the blood vessels that supply the muscles. A myopathy is a muscle disease, and inflammation is response to cell damage.

Another word for inflammatory myopathy is myositis. The *myo* root means muscle, and the *itis* root means inflammation; so a myositis is an inflammatory muscle disease.

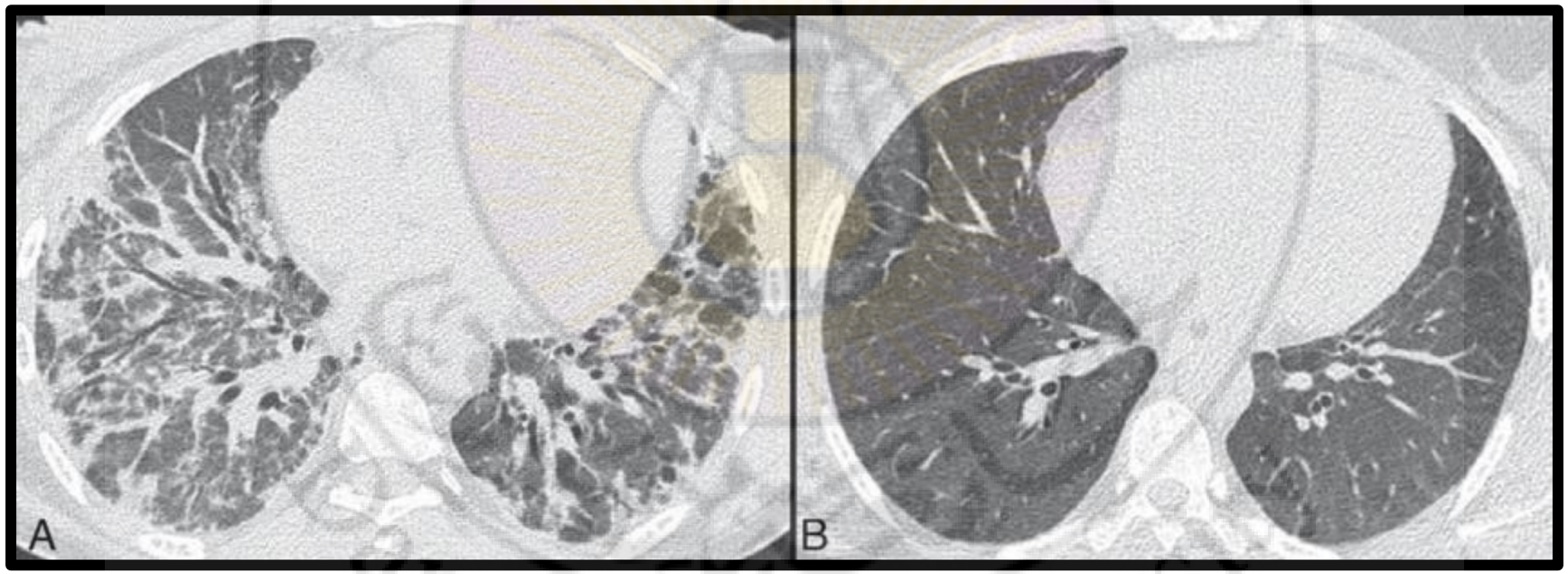
Muscle disease

Polymyositis and dermatomyositis



Muscle disease

Polymyositis and dermatomyositis



Bilateral subpleural and perilobar areas of airspace consolidation and ground-glass opacities. B. Follow-up CT scan performed 18 months later showing the disappearance of airspace consolidation, replaced by subtle groundglass opacities in the periphery of the lungs.

Muscle disease

Acquired non-inflammatory myopathy

Thyroid disorders

- ***Hypothyroidism***

-muscle weakness with muscle cramps, pain & stiffness in 1/3rd
- prolonged relaxation phase of muscle stretch reflexes
-Hoffman's syndrome: muscle enlargement (unknown cause), &weakness with muscle stiffness
-CK- usually >10x↑ed
-Biopsy : normal

- ***Hyperthyroidism***

-proximal weakness with atrophy
-sometimes bulbar, respiratory & esophageal muscle involvement : dysphagia, dysphonia, aspiration
-muscle stretch reflexes are often brisk
-CK: usually N
-Biopsy : atrophy of fibers

- Others:

- thyrotoxic periodic paralysis
- Grave's ophthalmopathy :progressive ophthalmopathy, with proptosis

Cont,d

- ***Hyperparathyoidism***

-proximal muscle weakness, muscle wasting, brisk stretch reflexes
-CK : usually N
-Biopsy : varying degrees of atrophy

- ***Hypoparathyoidism***

- Hypocalcemia resulting in sustained tetany & muscle damage
- Hypo- or areflexia
- CK : may be↑ed

- ***Diabetes mellitus***

- myopathy is uncommon
- rarely ischemic infarction of the thigh muscles
- abrupt onset of pain, tenderness, & edema of one thigh
- hard & indurated area on palpation

Dx- imaging / CT, MRI /
-focal abnormality in muscle

- ***Vitamin deficiency***

- myopathy is rare
- proximal muscle weakness
- CPEO
- Vit. D , Vit. E deficiency

Muscle disease

Acquired non-inflammatory myopathy

Toxic myopathies

- *Direct toxicity* : common
  : muscle breakdown, rhabdomyolysis & myoglobinuria may occur
  Ex.- lipid lowering agents, glucocorticoids - common
- *Drug induced autoimmune myopathy*
  Ex. – D-penicillamine : features similar to polymyositis

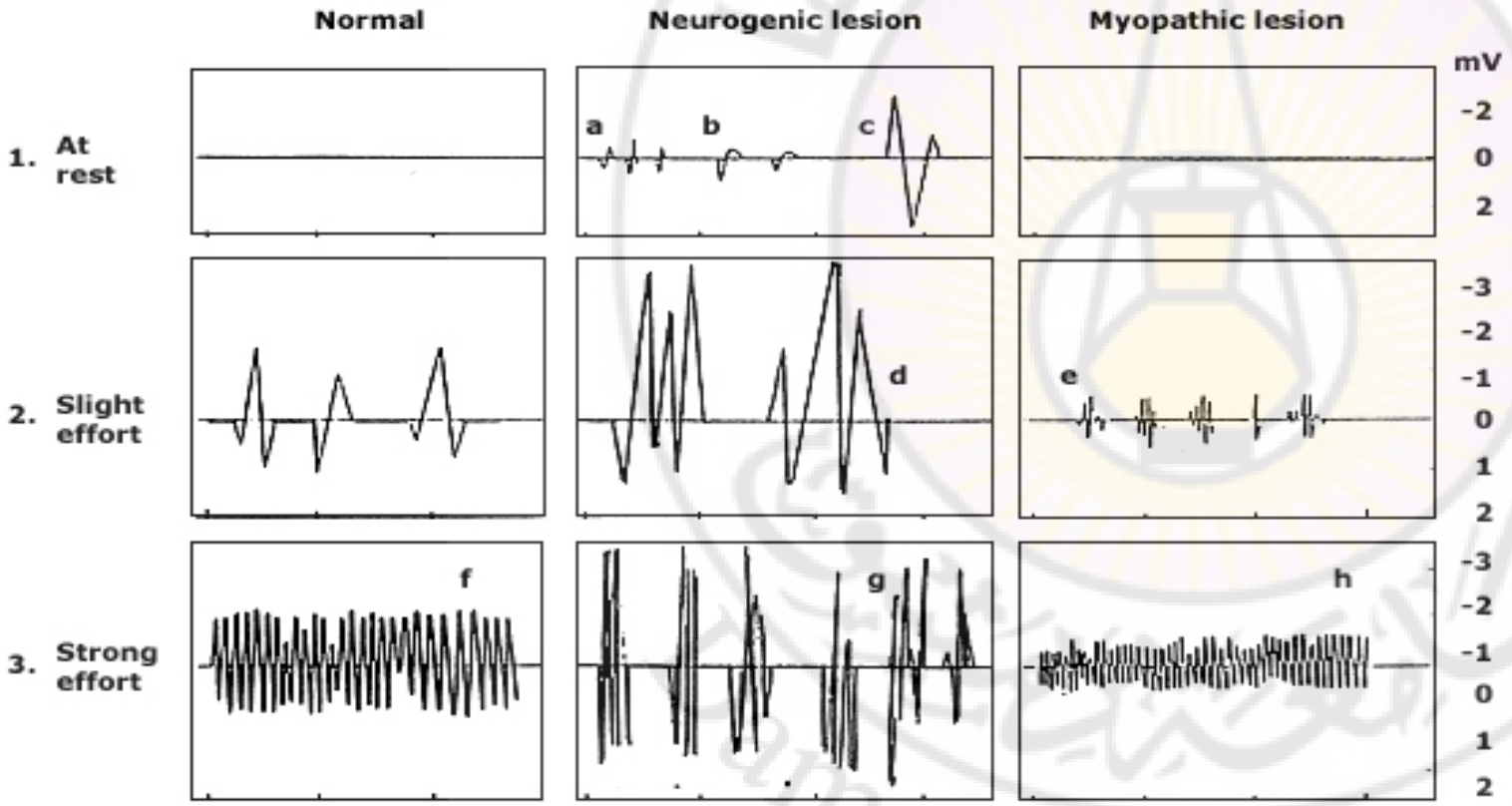
➢ ***Lipid lowering agents***

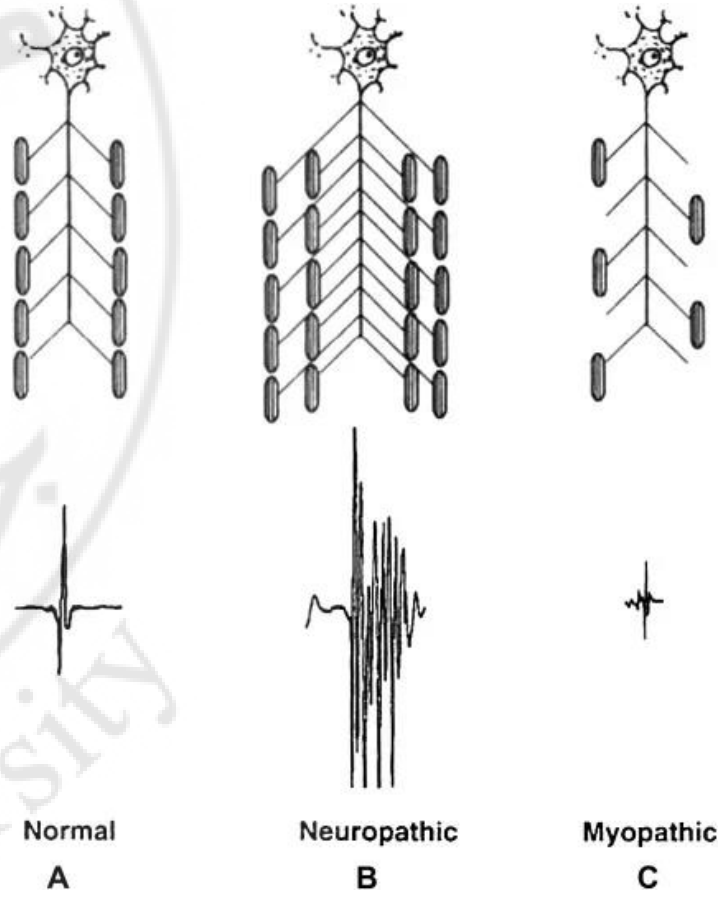
- all classes
- Sx - proximal weakness
  - myalgia, malaise, muscle tenderness
  - severe rxns : rhabdomyolysis & myoglobinuria
- Lab.- CK: elevated
  - EMG : myopathic
  - Biopsy : muscle necrosis
- Rx – cessation of drugs

Muscle disease

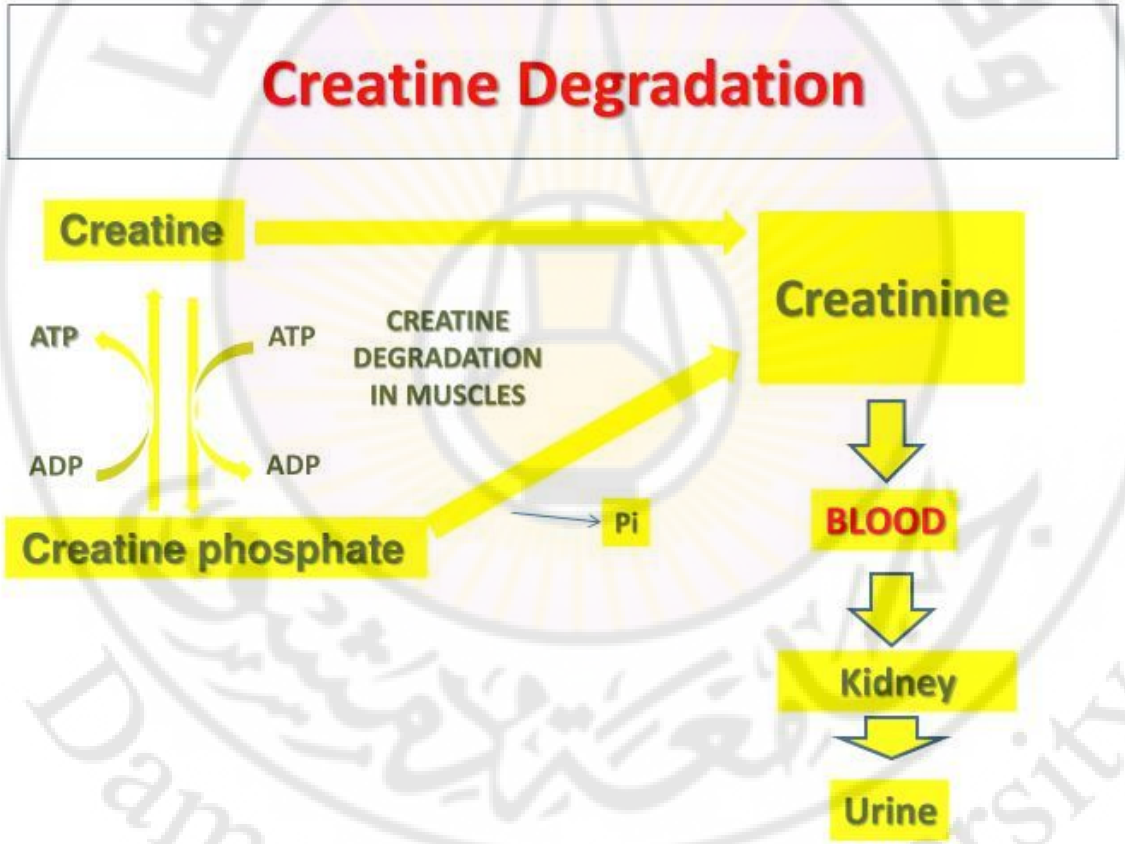
Test	Motor neurone disease	Peripheral neuropathy	Muscle disease
Biochemistry			
Creatine kinase	Normal	Normal	Elevated
Electrical studies			
Electromyography	Denervation	Denervation	Muscle disease
Motor and sensory nerve conduction studies	Normal	Delayed conduction velocities and reduced nerve action potentials	Normal
Histology **Histochemistry** **Immunofluorescence** **Electron microscopy**			
Muscle biopsy	Denervation	Denervation	Specific commentary on the nature of the muscle disease, i.e. dystrophy, polymyositis or acquired myopathy
Nerve biopsy		Sometimes helpful in establishing the precise cause of peripheral neuropathy	
Molecular genetics	No help in conventional MND	Helpful in hereditary motor and sensory neuropathy	Helpful in the inherited muscle diseases

Muscle disease





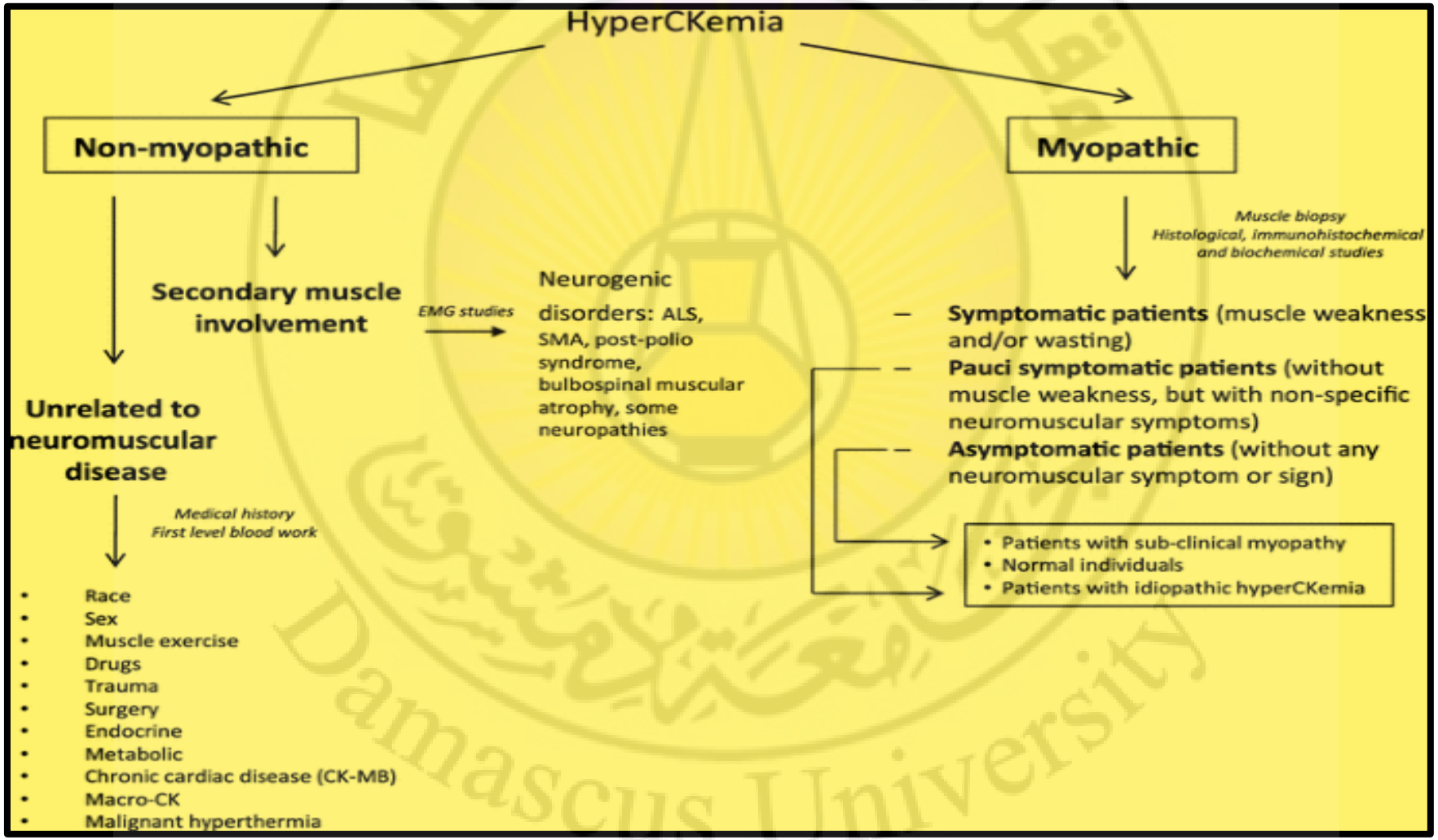
Muscle disease



Muscle disease

Isoenzyme name	Composition	Present in	Elevated in
CK-1	BB	Brain	CNS diseases
CK-2	MB	Myocardium / Heart	Acute myocardial infarction
CK-3	MM	Skeletal muscle, Myocardium	

Muscle disease

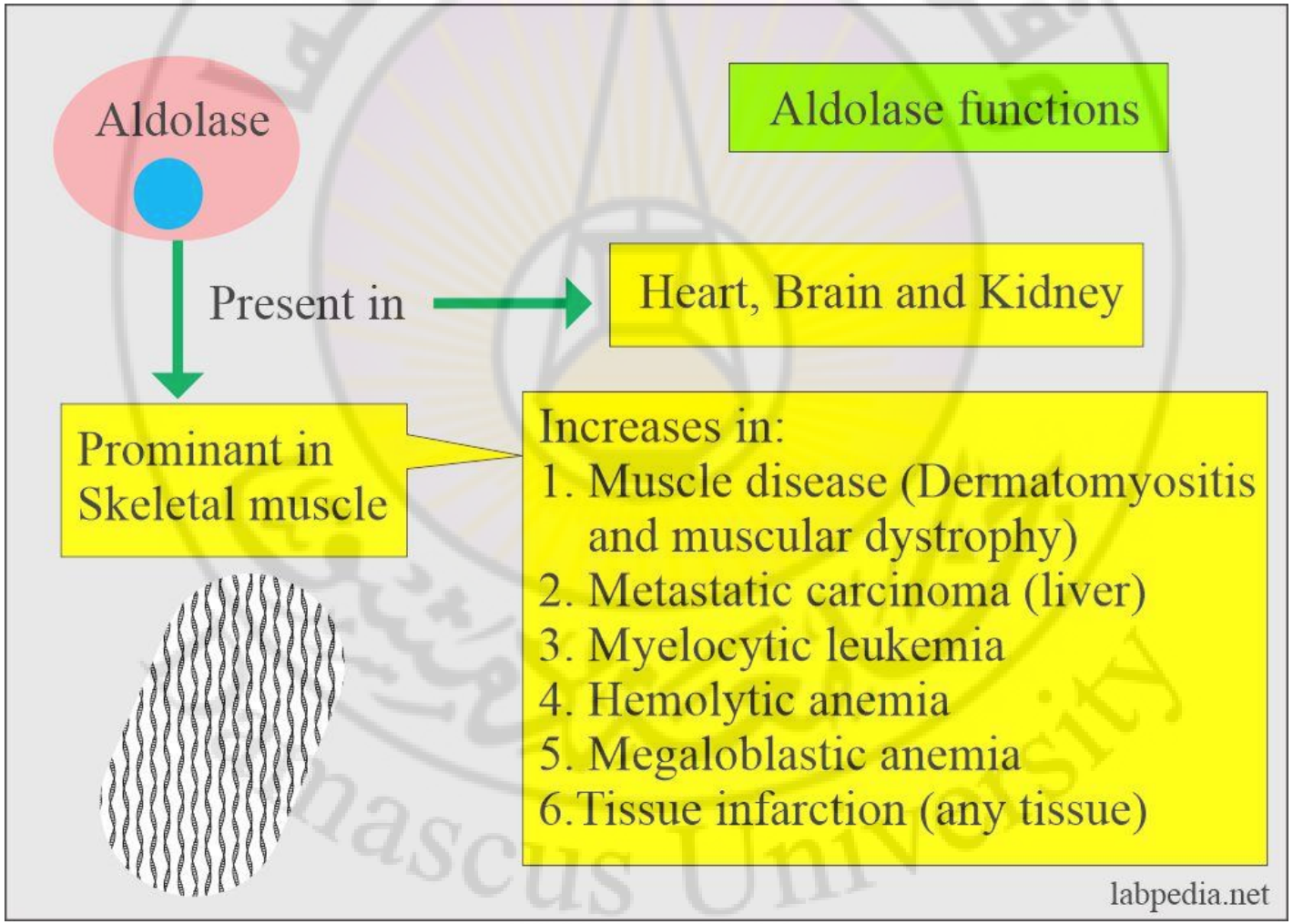


Muscle disease

- LDH-1: heart and red blood cells
- LDH-2: white blood cells
- LDH-3: lungs
- LDH-4: kidneys, placenta, and pancreas
- LDH-5: liver and skeletal muscle

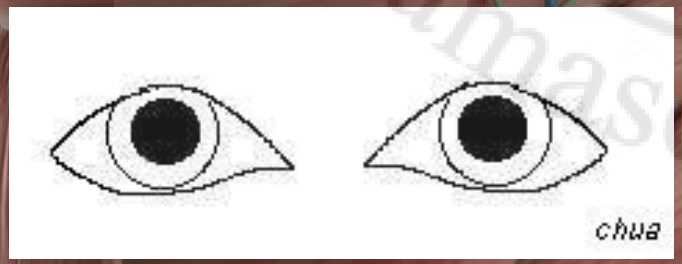
The LDH test is generally used to screen for tissue damage

Muscle disease



بسم الله الرحمن الرحيم

Myasthenia Gravis (Goldflam diseas)

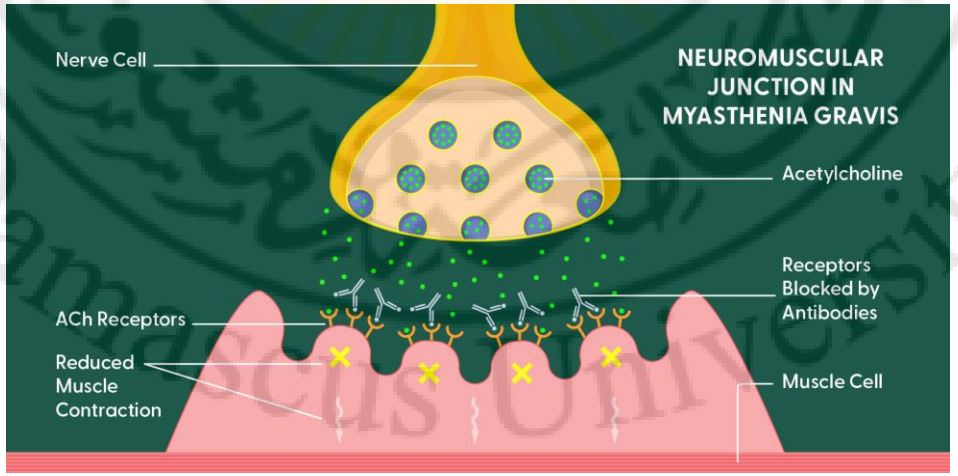


Prof. Mohamad Shehadeh Agha
MD MRCP (London) FRCP (Edin)

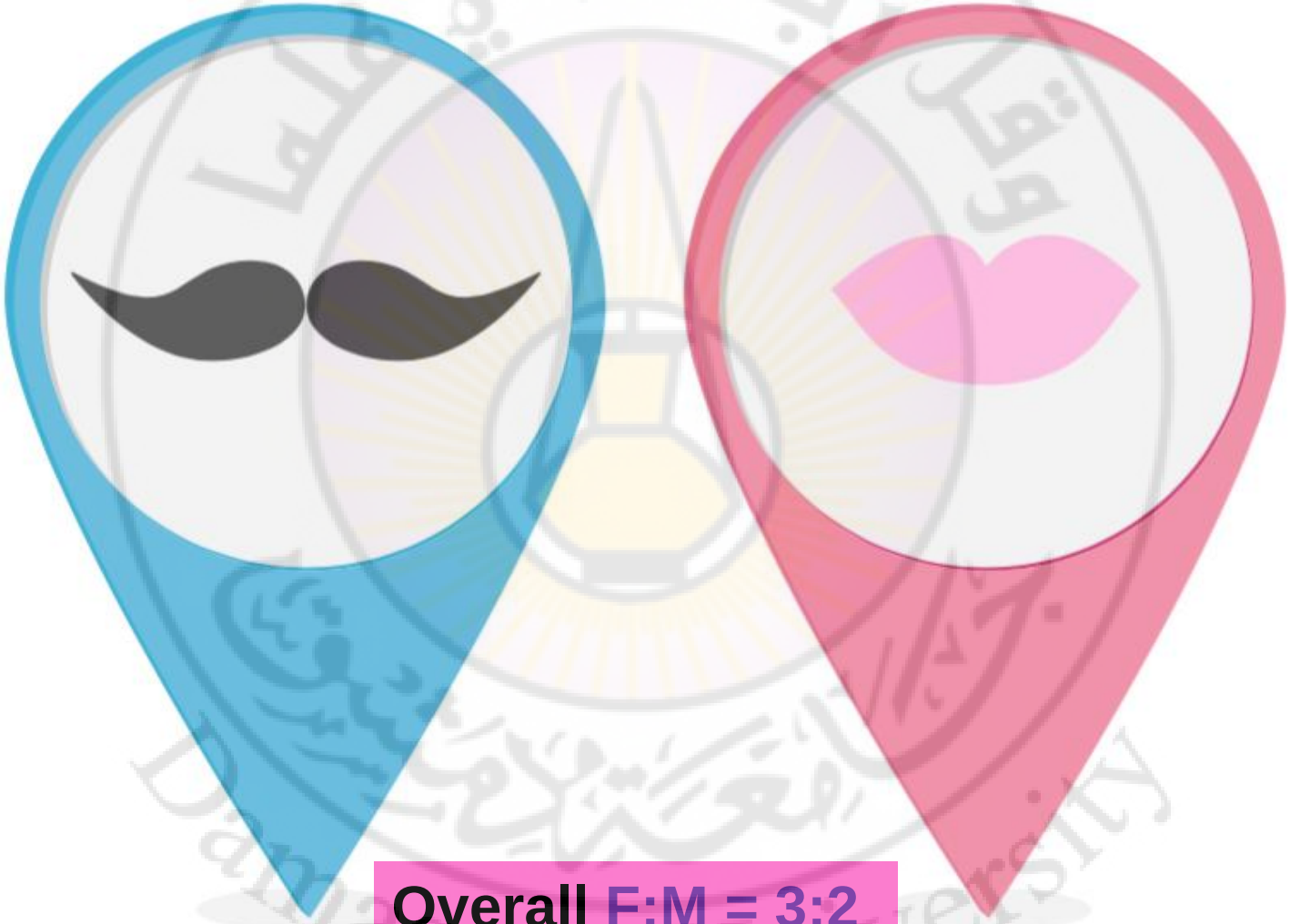
INTRODUCTION

An Immunologic Mechanism

Failure of effective neuromuscular transmission on the postsynaptic side



When <40 yrs f:m = 2-3:1, males more affected in elderly(3:2)



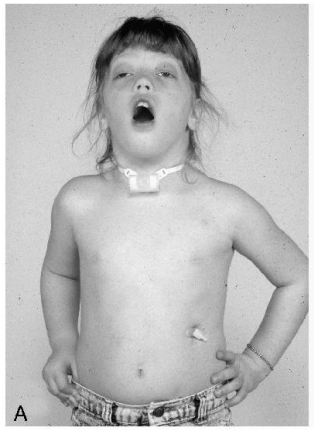
Overall F:M = 3:2

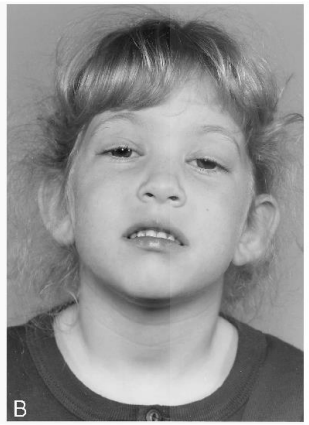
BIMODAL PEAK

50-60 yrs(older men)

20-30 yrs(young women)

< 10% occur in children **<10** yrs





Congenital type :

Maternal MG usually not present

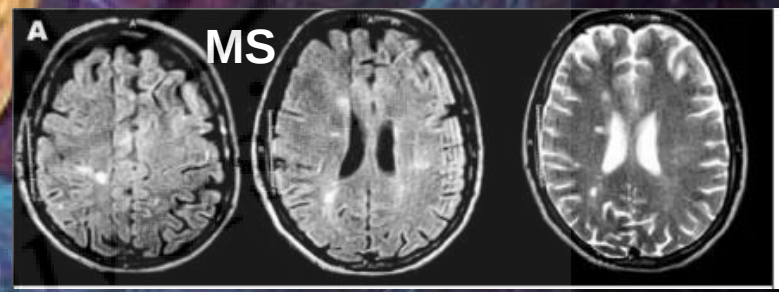
Onset at birth with ocular or generalized weakness

The course of weakness usually fixed

Family history often present

Anti Ach R antibodies not present

More common is a family history of one or the **other autoimmune diseases**, and suggests partial **genetic predisposition**

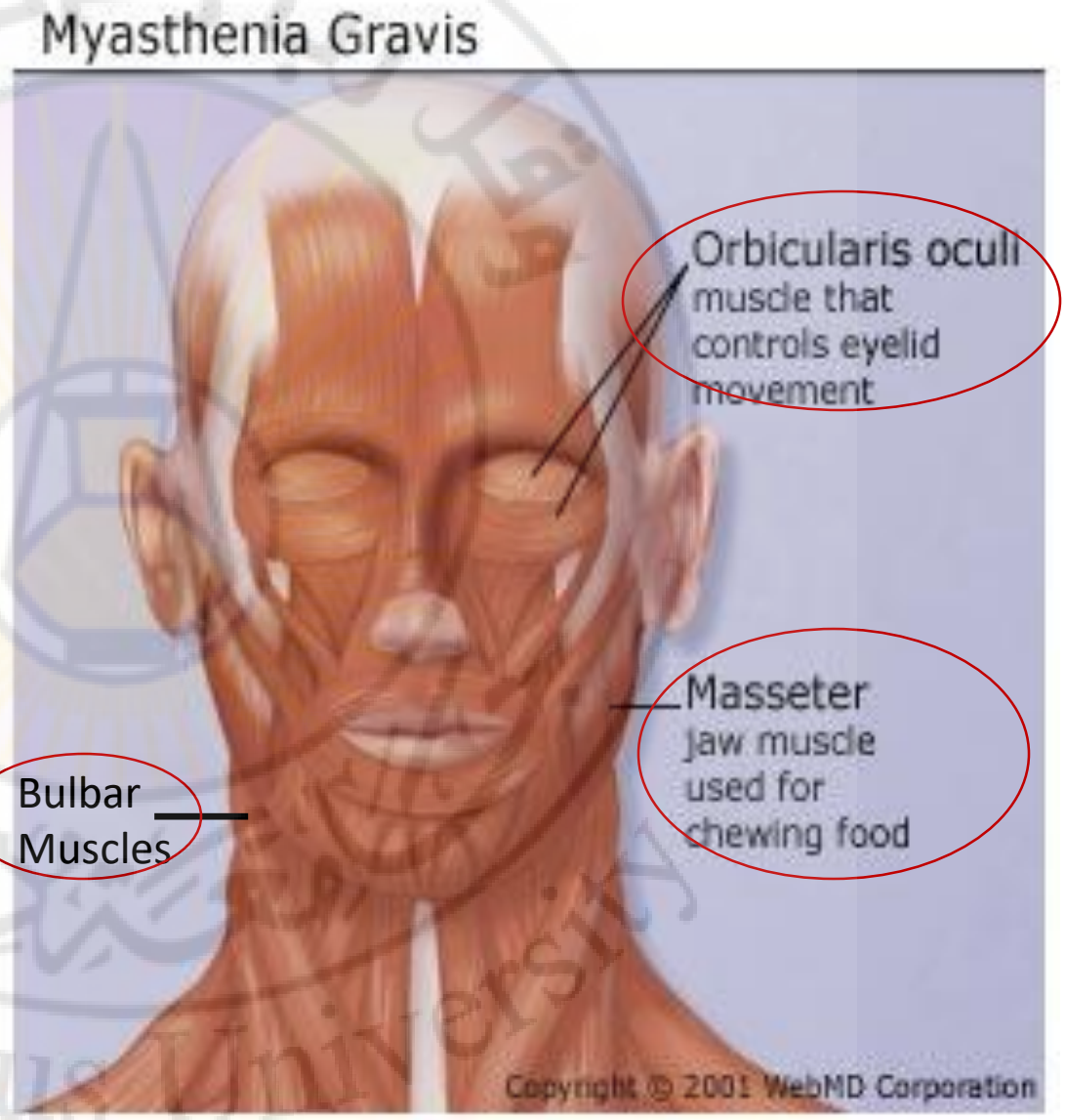


CLINICAL PRESENTATION

CLINICAL PRESENTATION

MUSCLE STRENGTH

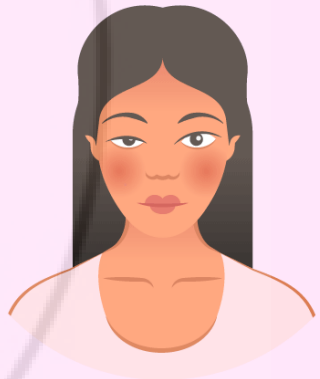
- Ocular muscle weakness
- Facial muscle weakness
- Bulbar muscle weakness
- Limb muscle weakness
- Respiratory weakness



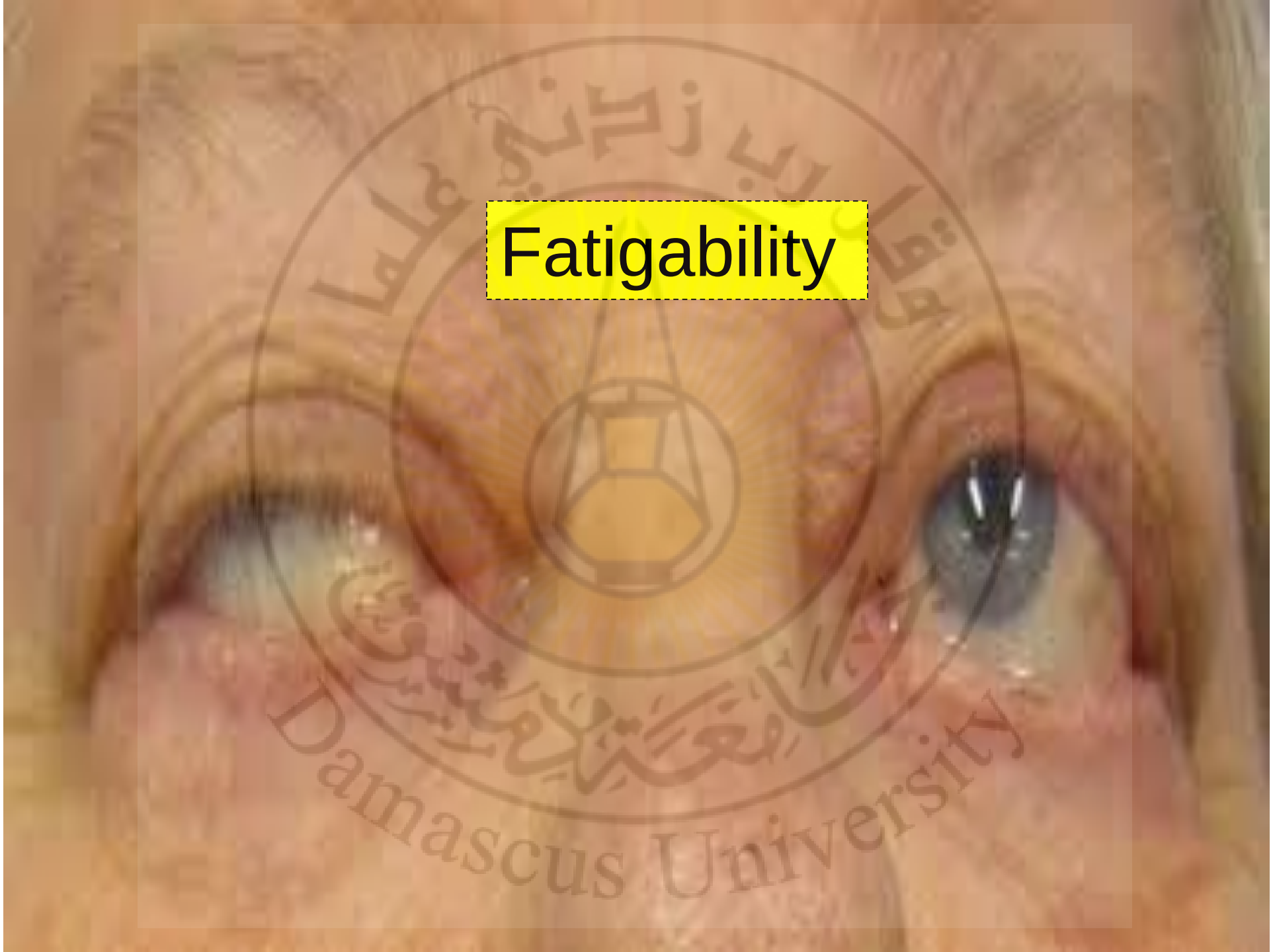
Ocular Muscles

Muscle weakness

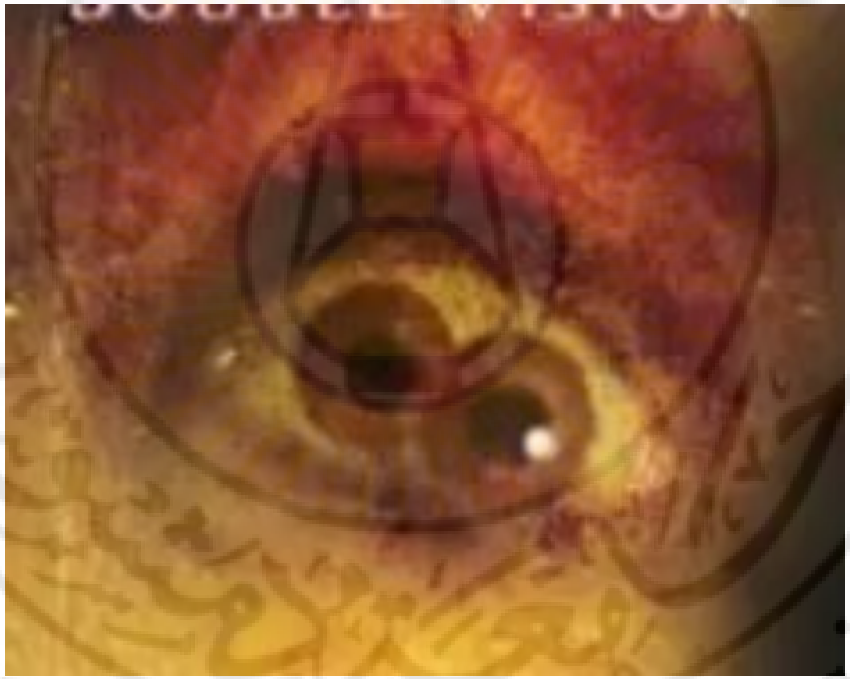
Double vision

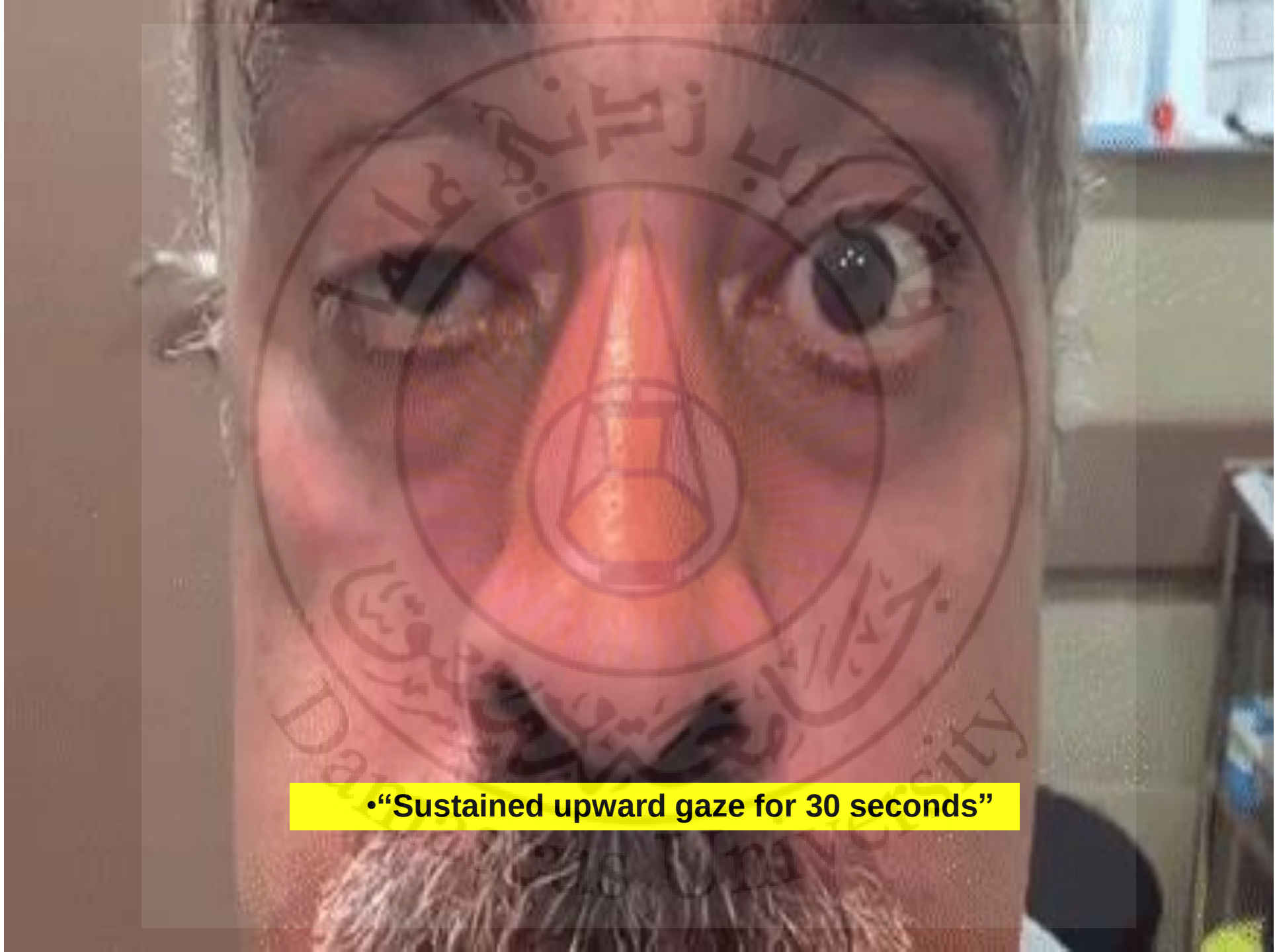


Drooping eyelids


Fatigability

Fluctuating weakness increased by exertion



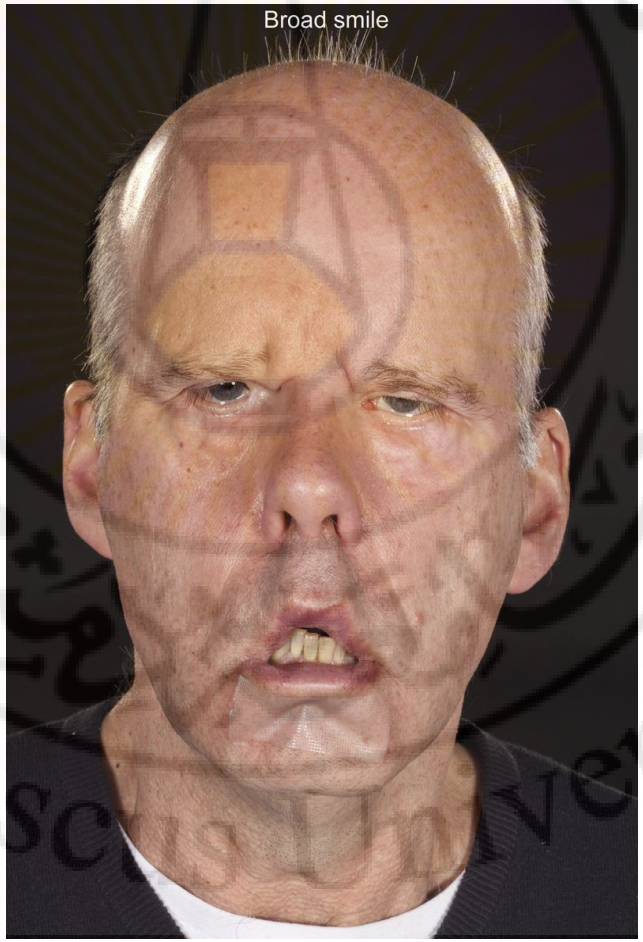


•“Sustained upward gaze for 30 seconds”

Myasthenia Gravis (MG disease)

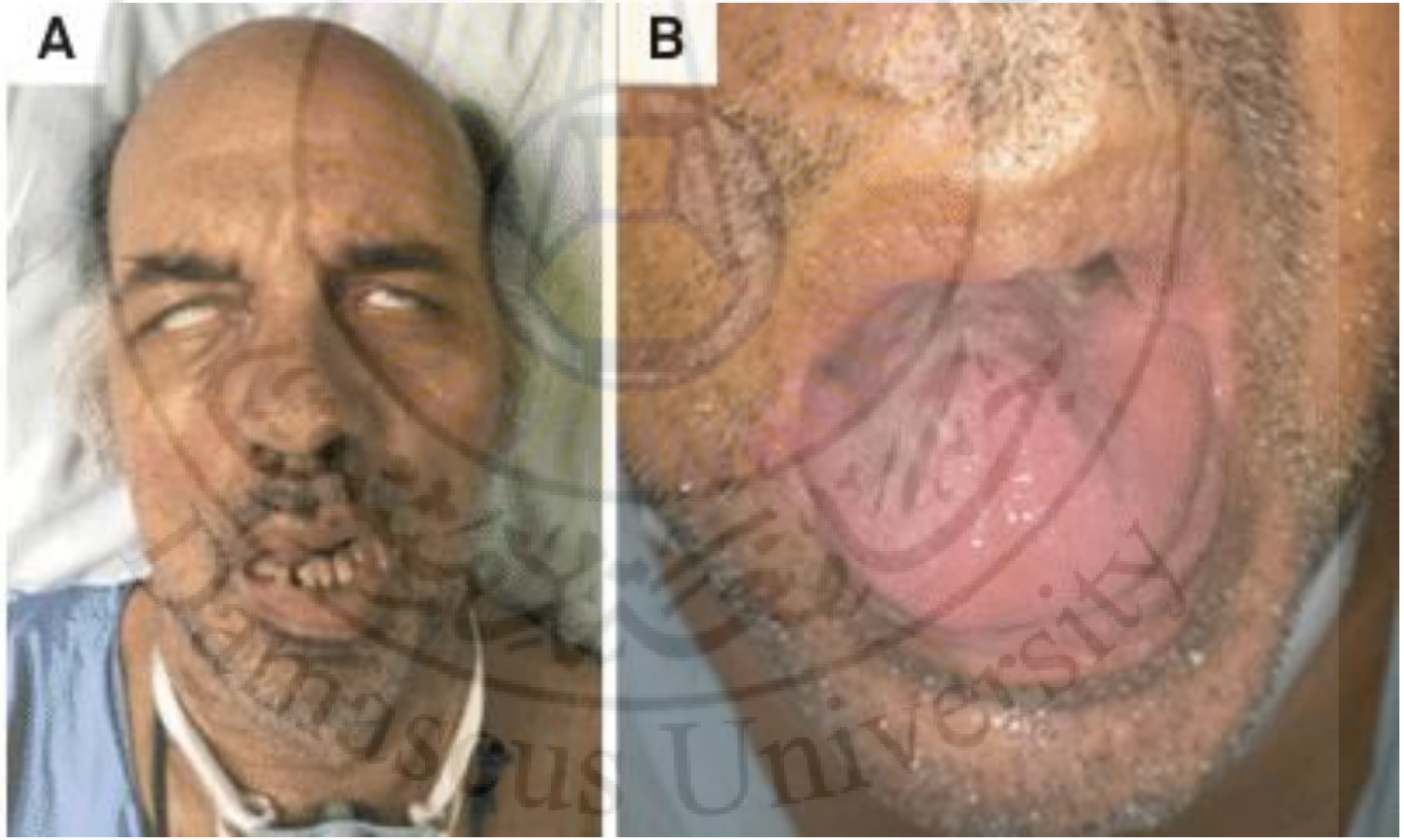
2. FACIAL MUSCLE WEAKNESS

Facial muscle weakness is almost always present

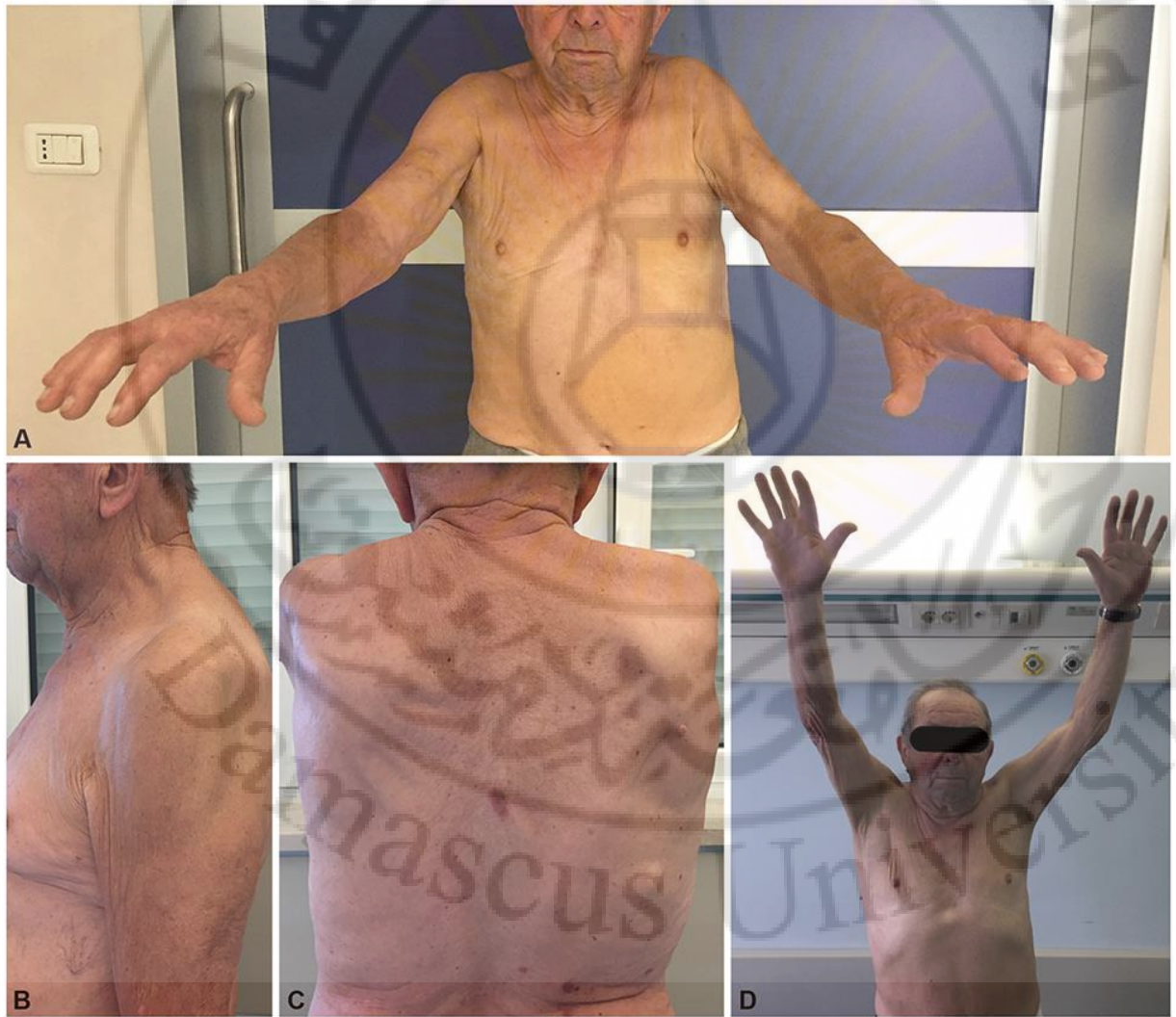


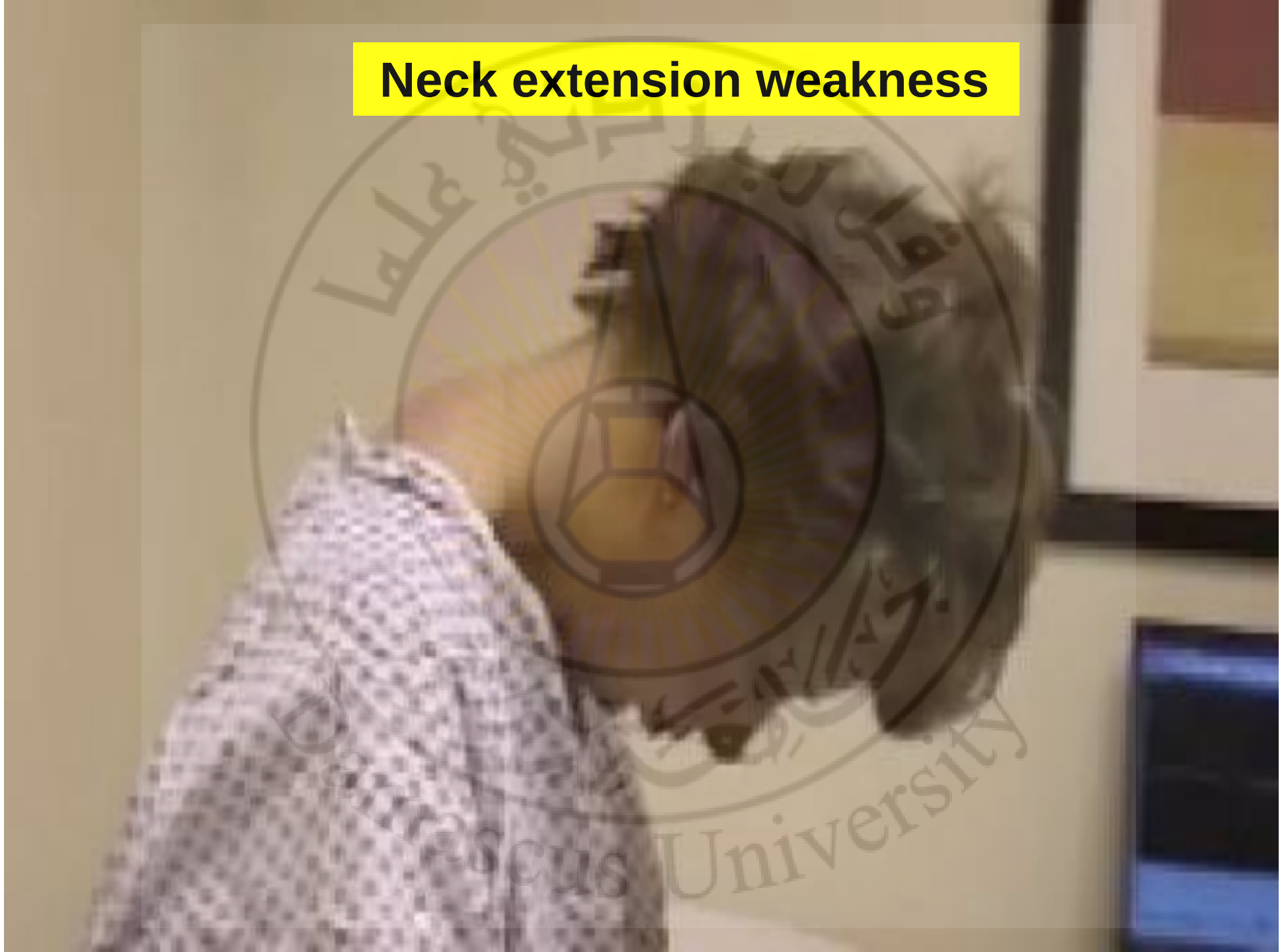
3. BULBAR MUSCLE WEAKNESS

Bulbar muscle weakness
(more in **Anti MuSK Ab** positive cases)



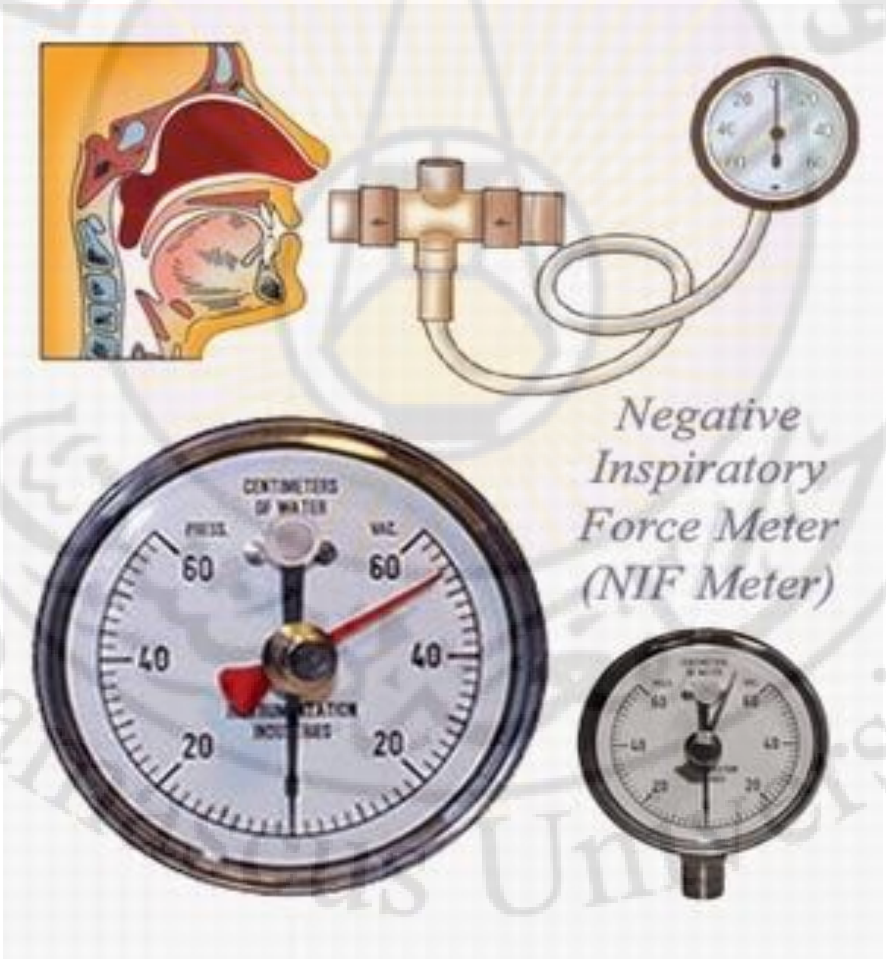
4. LIMB MUSCLE WEAKNESS




Neck extension weakness

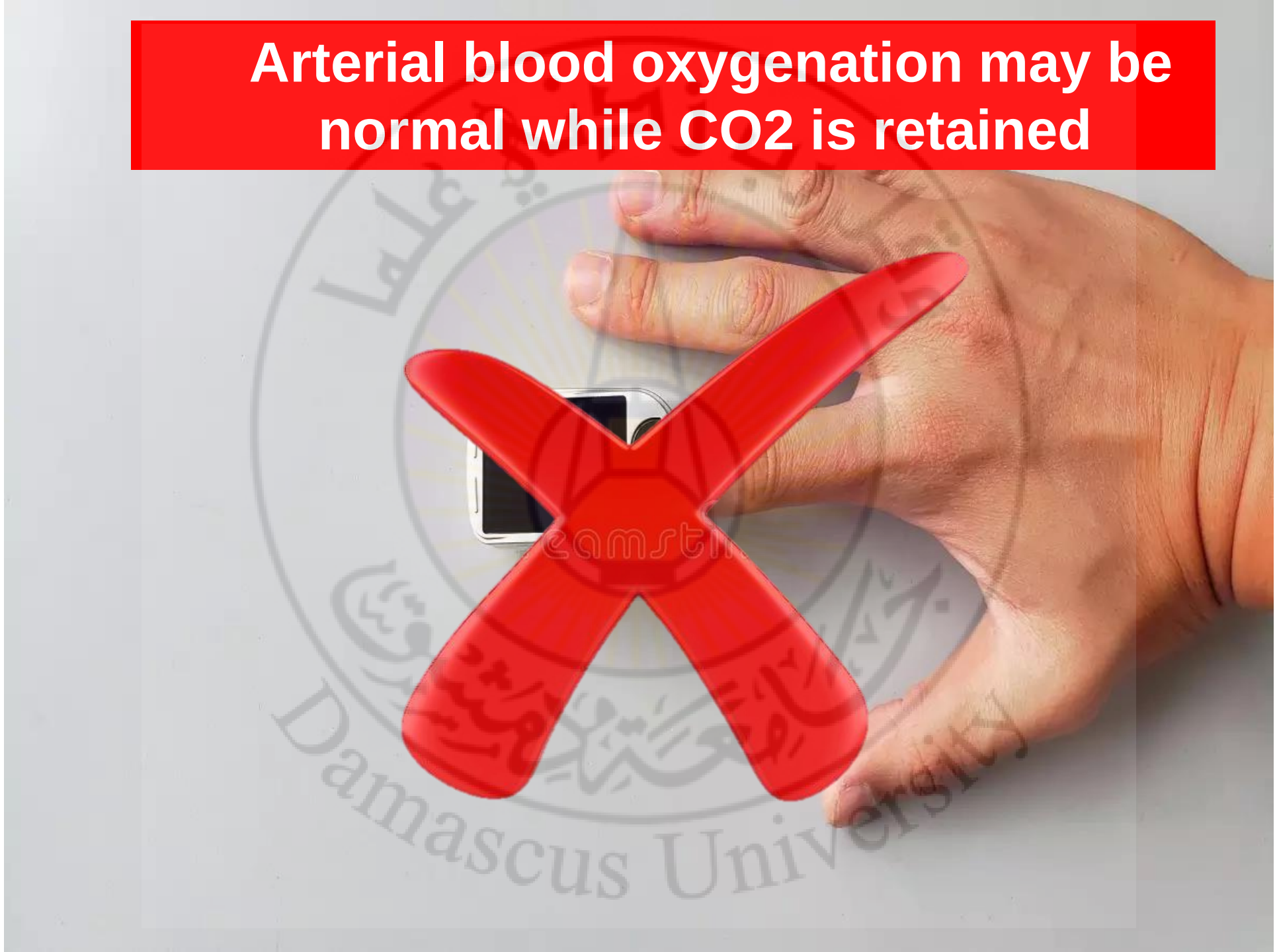
5. RESPIRATORY MUSCLE WEAKNESS

- **Monitor negative inspiratory force, vital capacity and tidal volume**



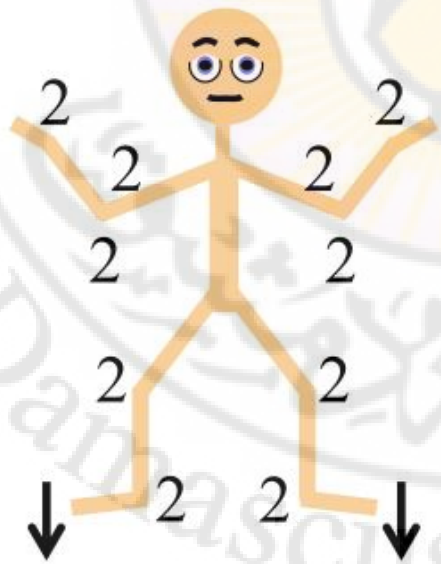
Do NOT rely on pulse oximetry

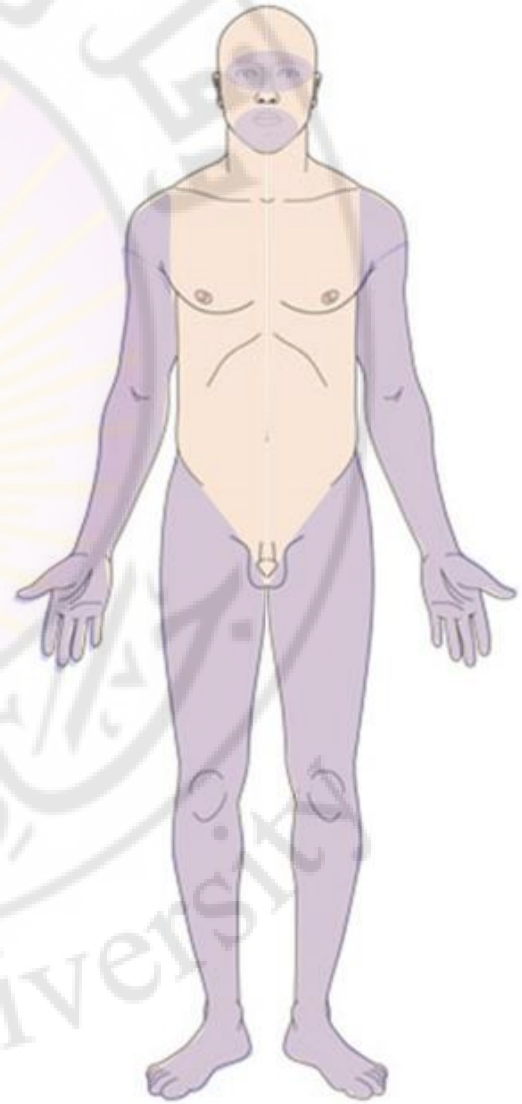
Arterial blood oxygenation may be normal while CO2 is retained

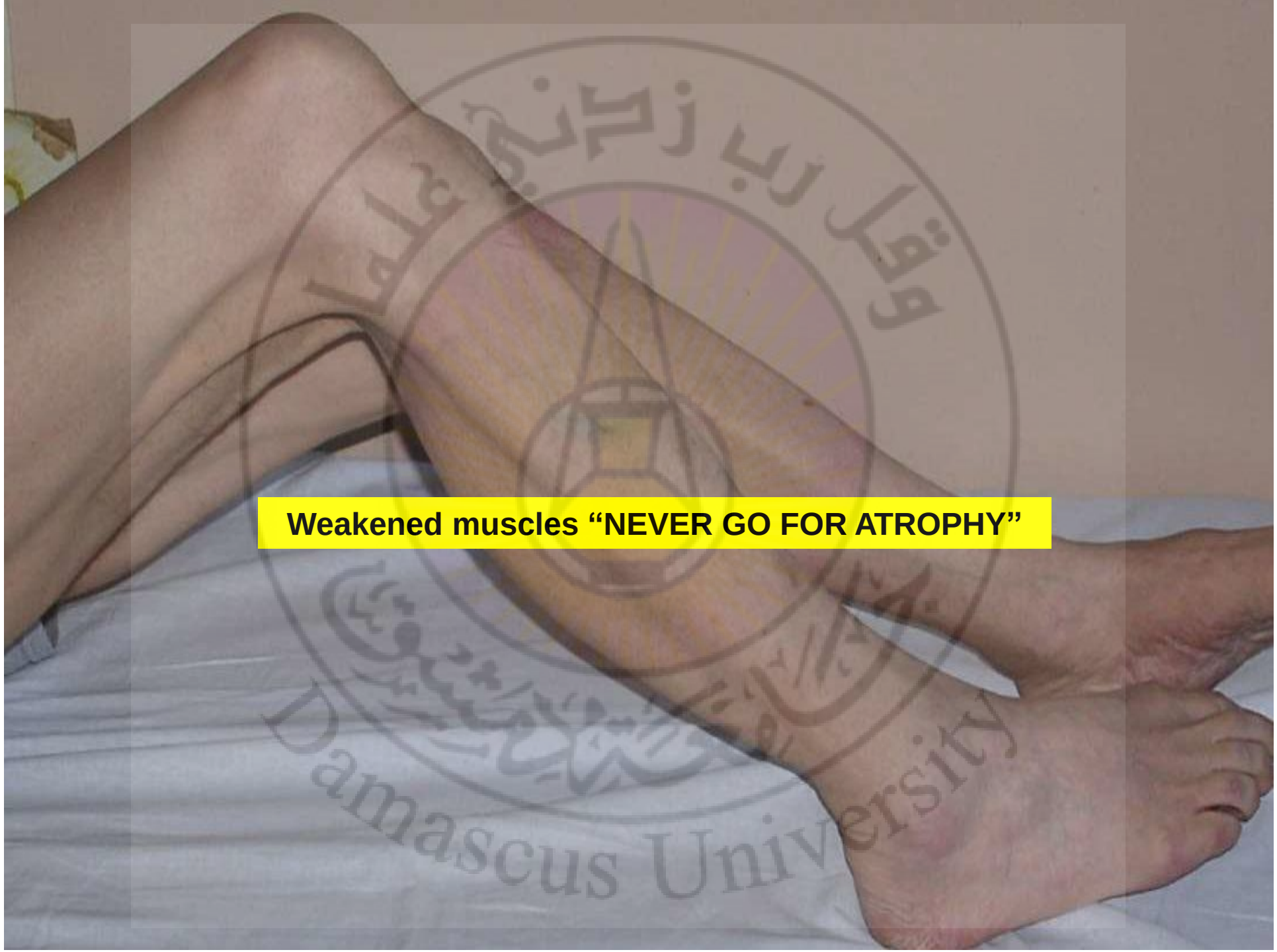


Pattern: Bilateral, symmetric weakness without numbness with ocular or bulbar muscle weakness

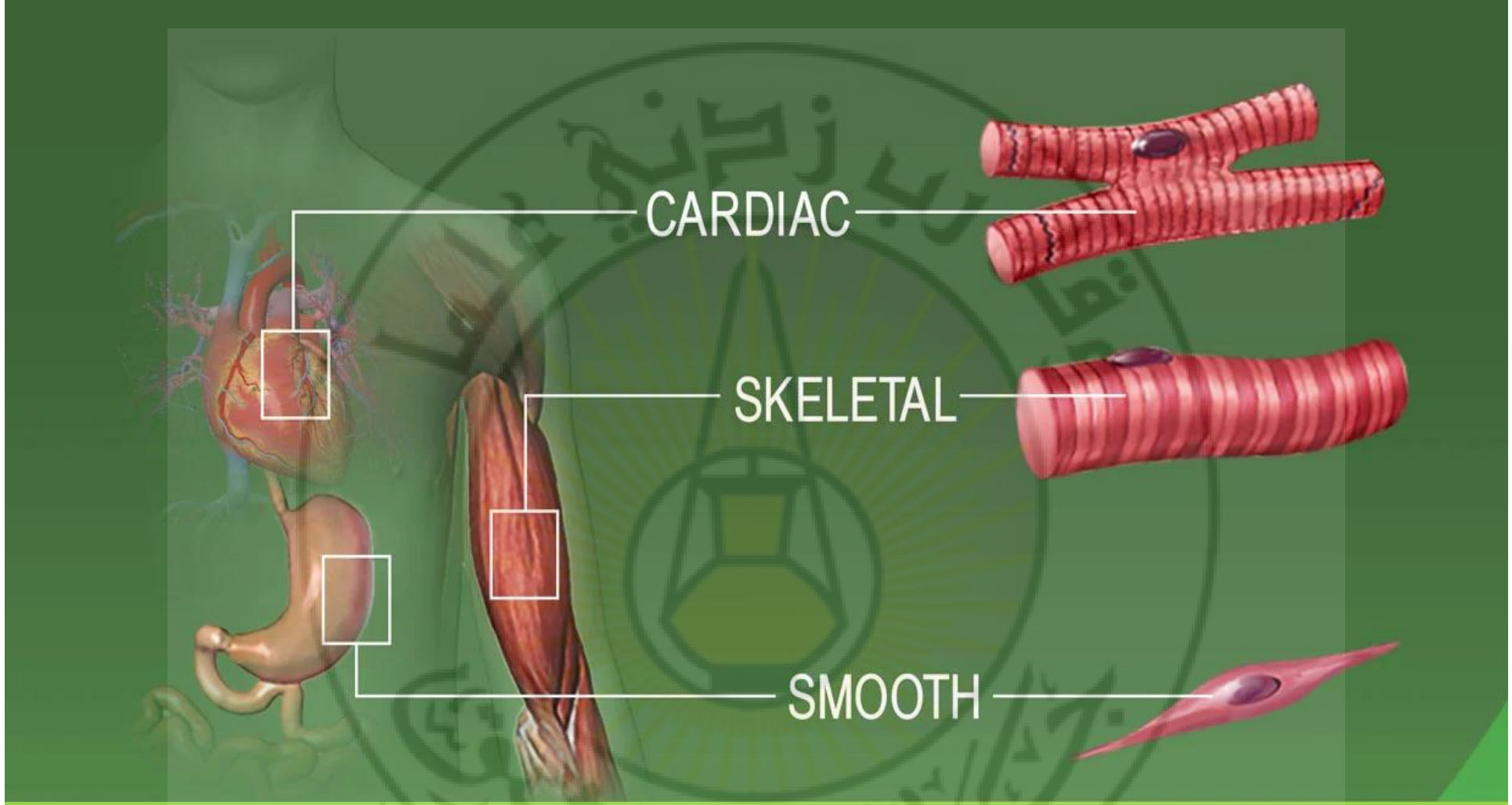
Myasthenia Gravis



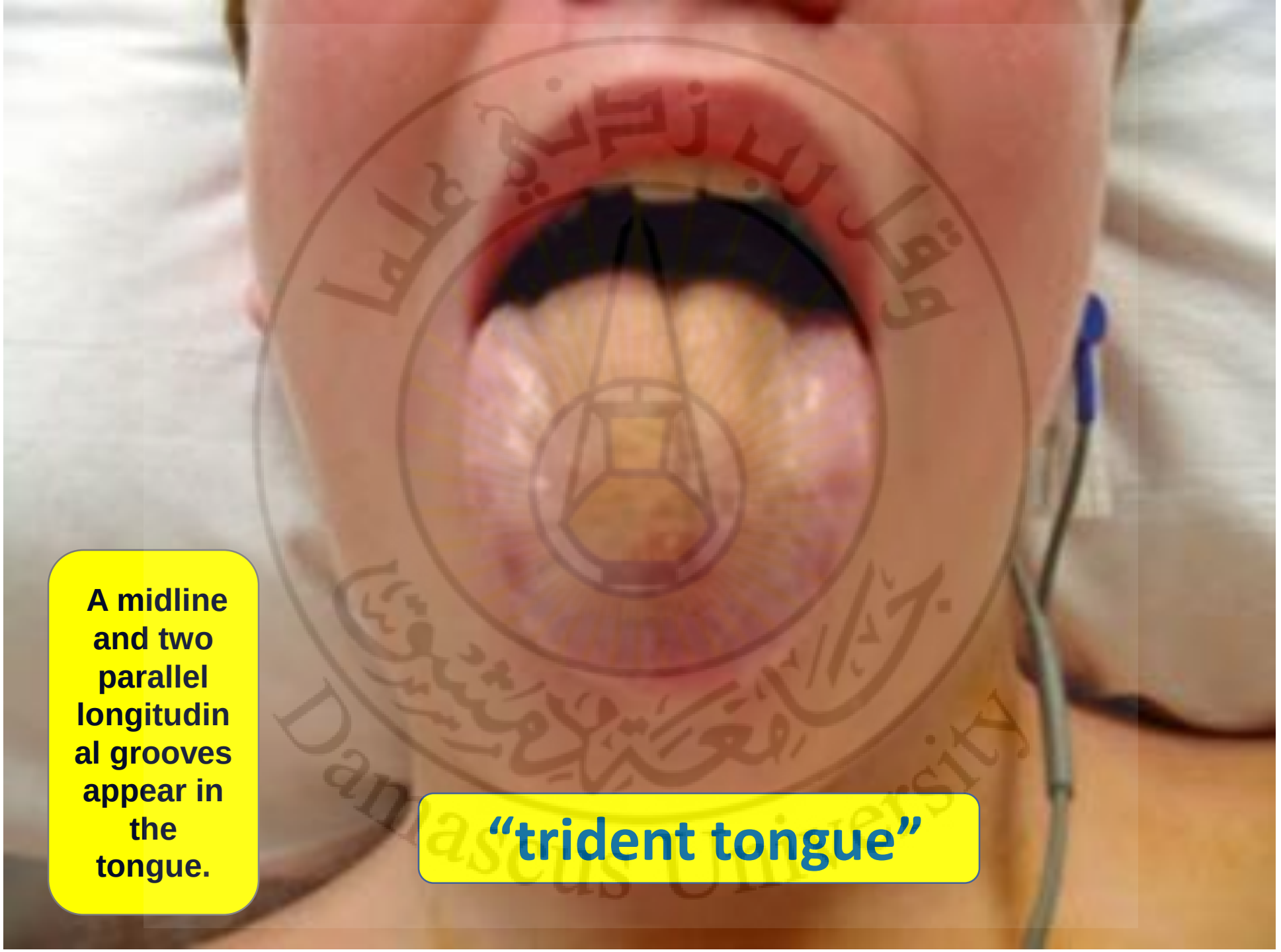



Weakened muscles “NEVER GO FOR ATROPHY”

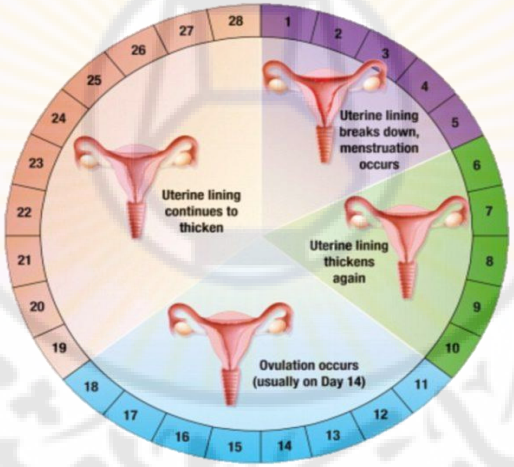
Tendon Reflexes are normal



Smooth and cardiac muscles are not involved


A midline and two parallel longitudinal grooves appear in the tongue.
“trident tongue”

A temporary increase in weakness may follow vaccination, menstruation and exposure to extremes of temperature



DRUGS PRECIPITATING MYASTHENIA

Anti-infective Agents	Cardiovascular Agents	Other Agents
Aminoglycosides	**Propranolol**	**Chloroquine**
Ampicillin	**Verapamil**	**Corticosteroids**
Ciprofloxacin	**Quinidine**	**"d-penicillamine"**
Erythromycin	**Procainamide**	**Phenytoin**
Imipenem	**Propafenone**	**Mydriatics**
Kanamycin	Acebutolol	Trihexyphenidyl
Pyrantel	Practolol	Interferon
	Timolol	Trimethadione
	Oxyprenolol	

PROGRESSION OF DISEASE

Spreads from ocular to facial to bulbar to truncal and limb muscles

Mild to severe…..over weeks to months

REMISSIONS

- Spontaneous remissions rare, most remissions with treatment occur within the **first three years**
- If remission lasts >1 yr and recurs disease tend to be progressive.
- Isolated ocular myasthenia > 1 yr, subsequent generalisation is only 16%
- The course is altered by thymectomy (even drug free remissions)


الآن يمكنك النوم بشكل هادئ
وطبيعي
SLEEP
STUDY

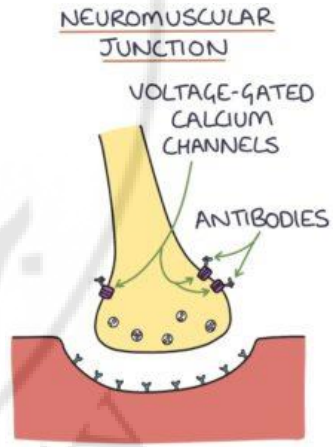
NEUROLOGIC CONDITIONS MIMICKING MYASTHENIA GRAVIS

CONDITION	SIGNS AND SYMPTOMS
ALS	Asymmetric muscle weakness and atrophy
Botulism	Generalized limb weakness
Guillain-Barré syndrome	Ascending limb weakness
Inflamm. muscle disorders	Proximal symmetric limb weakness
Lambert-Eaton syndrome	Proximal symmetric limb weakness
Multiple sclerosis	Bilateral internuclear ophthalmoplegia
Periodic paralysis	Intermittent generalized muscle weakness
Thyroid disease	
Congenital myasthenic syndromes	
Brainstem syndromes/encephalitis	

LAMBERT-EATON SYNDROME

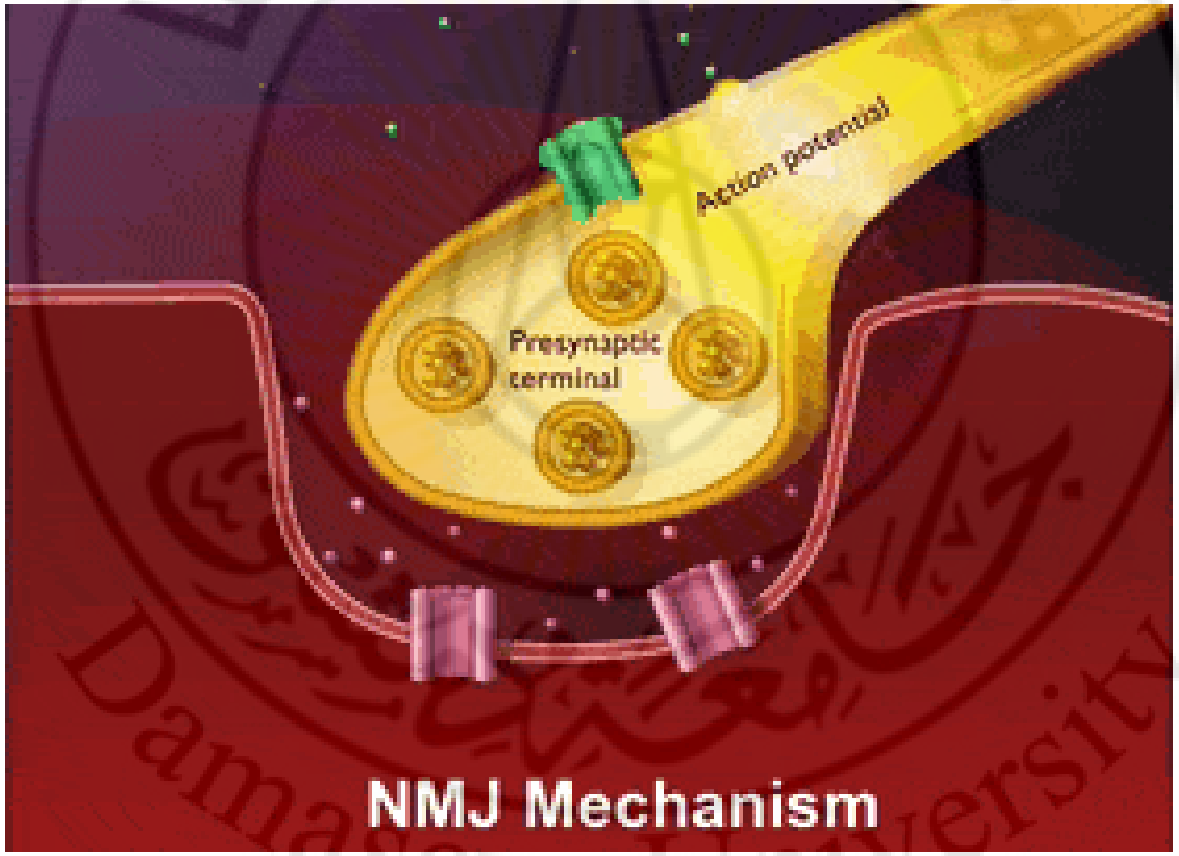
- **Presynaptic** disorder of NMJ
- Antibodies against **P/Q type calcium channels** at the motor nerve terminals (+ve in **85%**)
- **Impaired release** of Ach from nerve terminals
- Muscle weakness similar t MG (proximal>distal, CN involvement >70%)
- **"Warming up"** phenomenon

Depressed/absent reflexes
Autonomic changes
Incremental response to RNS

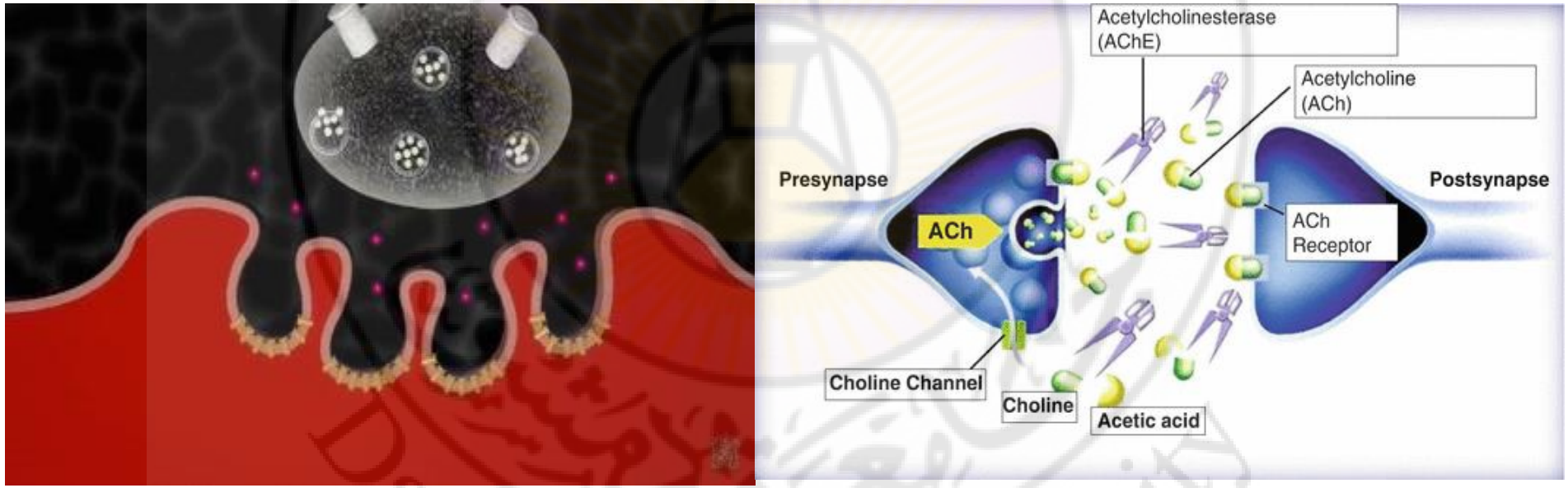


- Associated with Ca Lung(small cell Ca).. **"paraneoplastic"**
- Treatment: Immunosuppression; plasmapheresis; 3,4-DAP; pyridostigmine

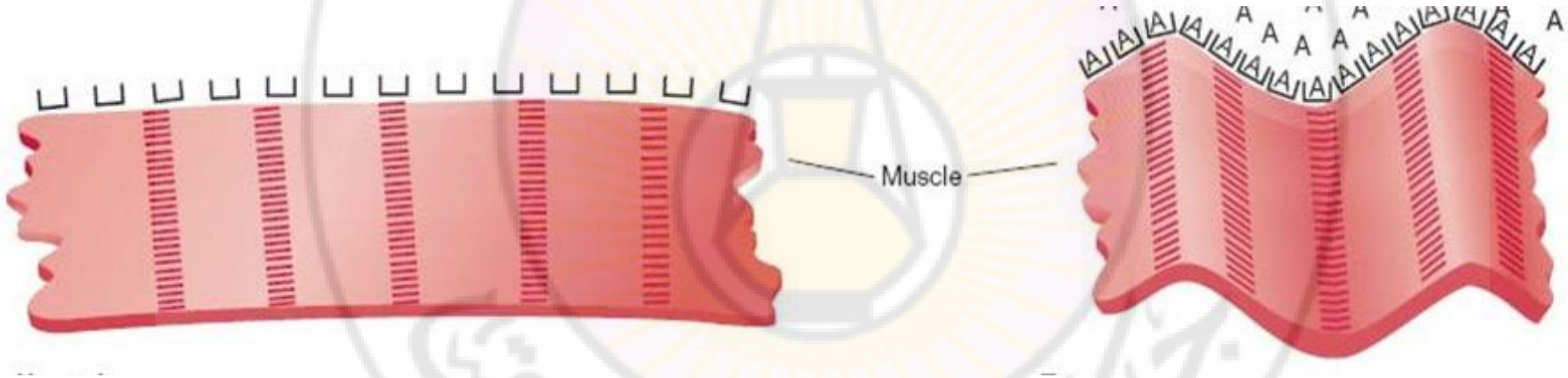
THE NEUROMUSCULAR JUNCTION



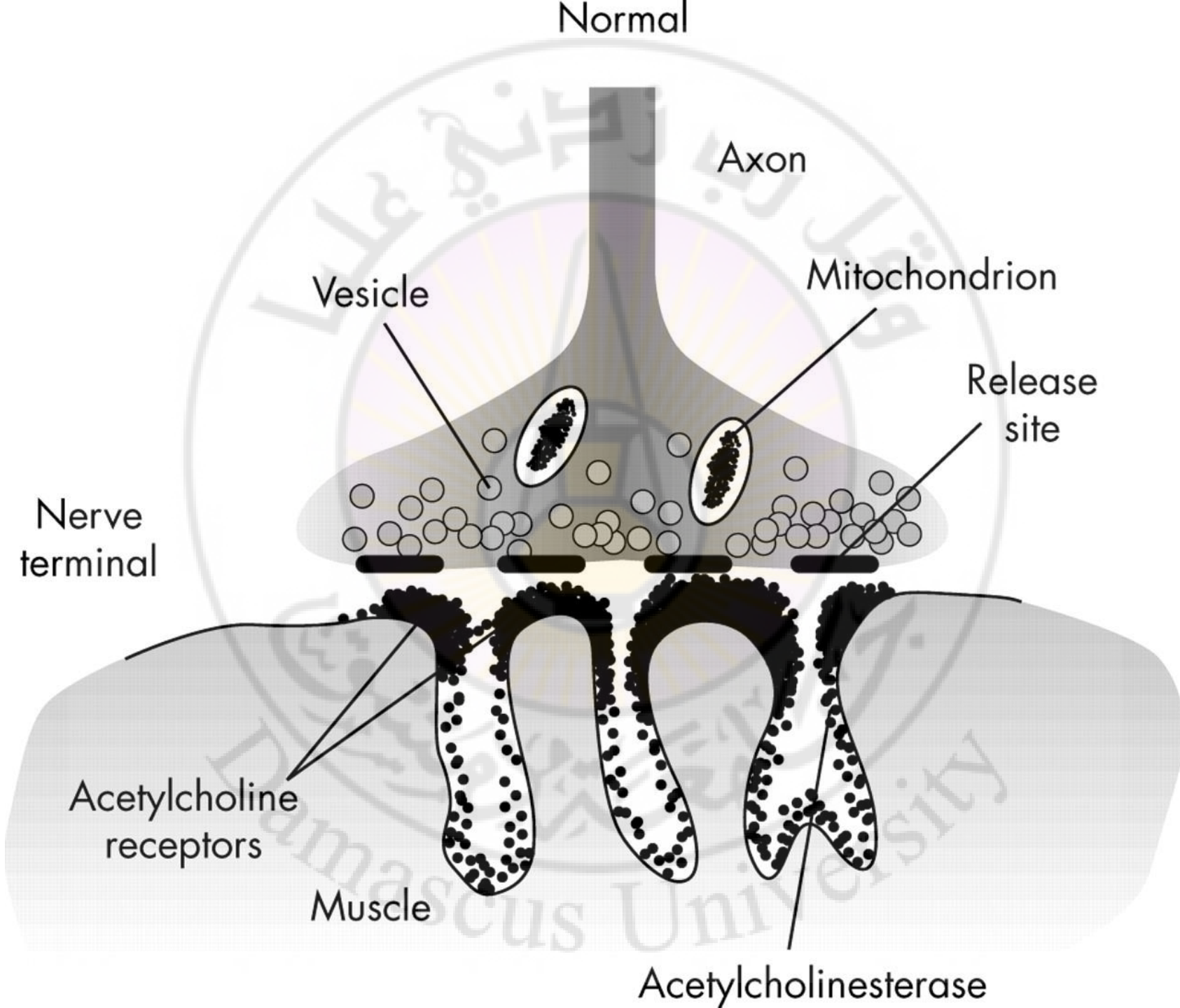
ACh molecules are hydrolyzed by the enzyme acetylcholinesterase (AChE), which is abundantly present at the NMJ.



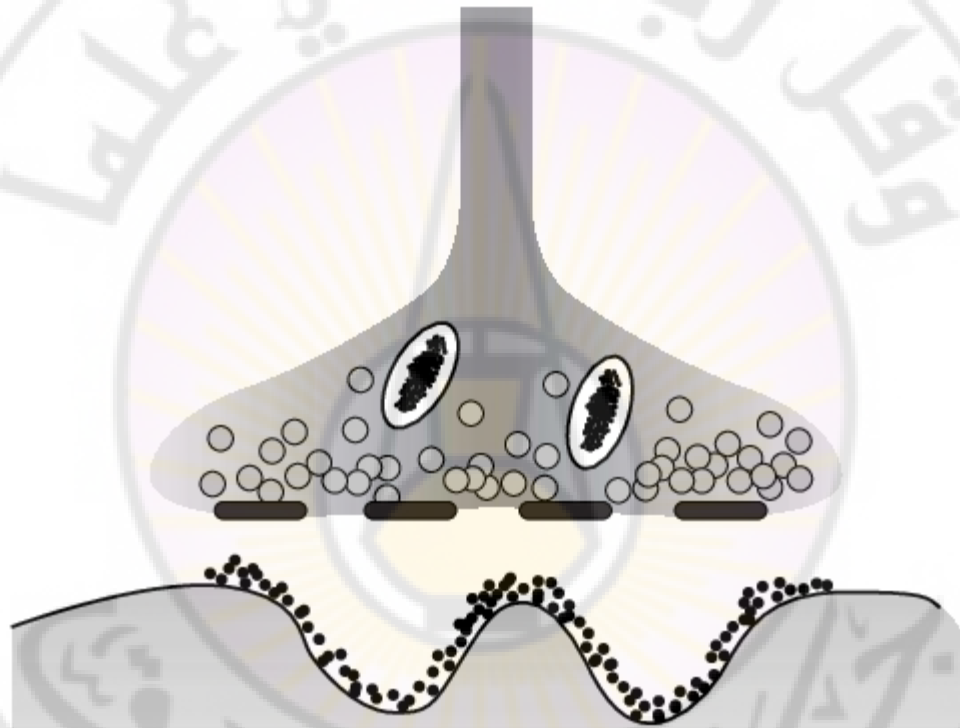
The surface area of the postsynaptic membrane is increased by infolding of the membrane adjacent to the nerve terminal.

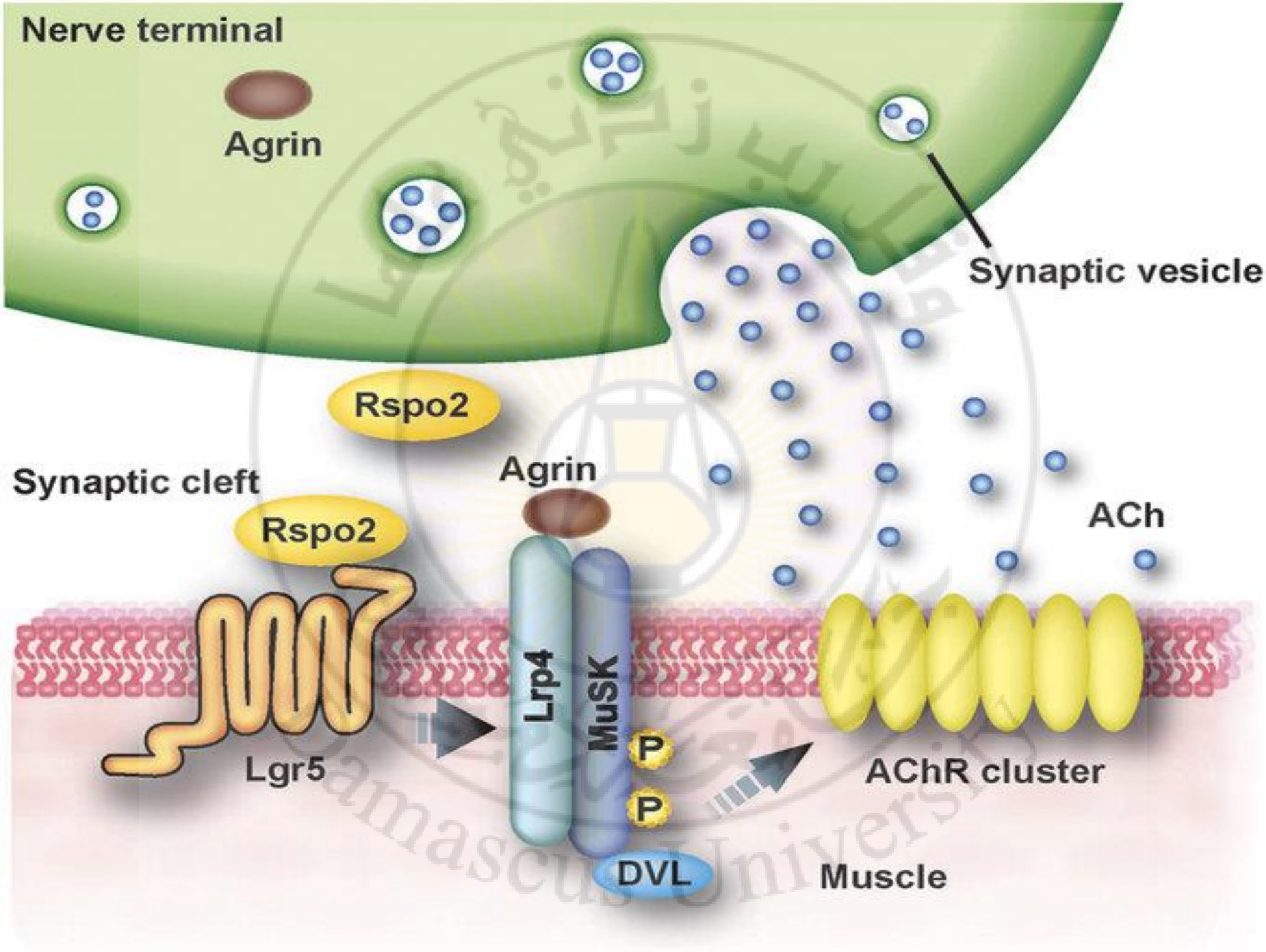


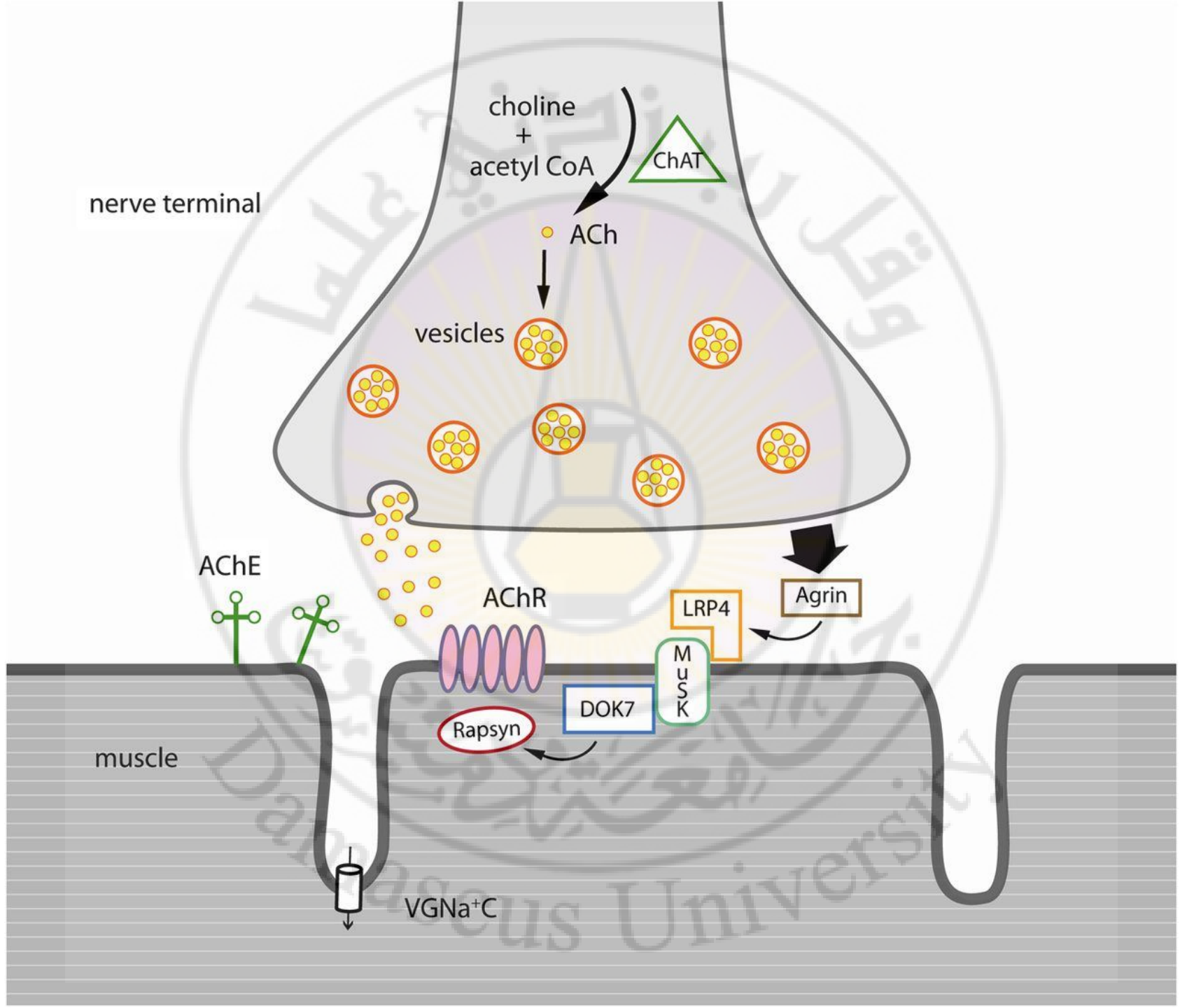
This increase in surface area enables the NMJ to utilize the ACh fully. AChRs are present in small quantities over most of the muscle membrane surface but are concentrated heavily at the tips of the NMJs.

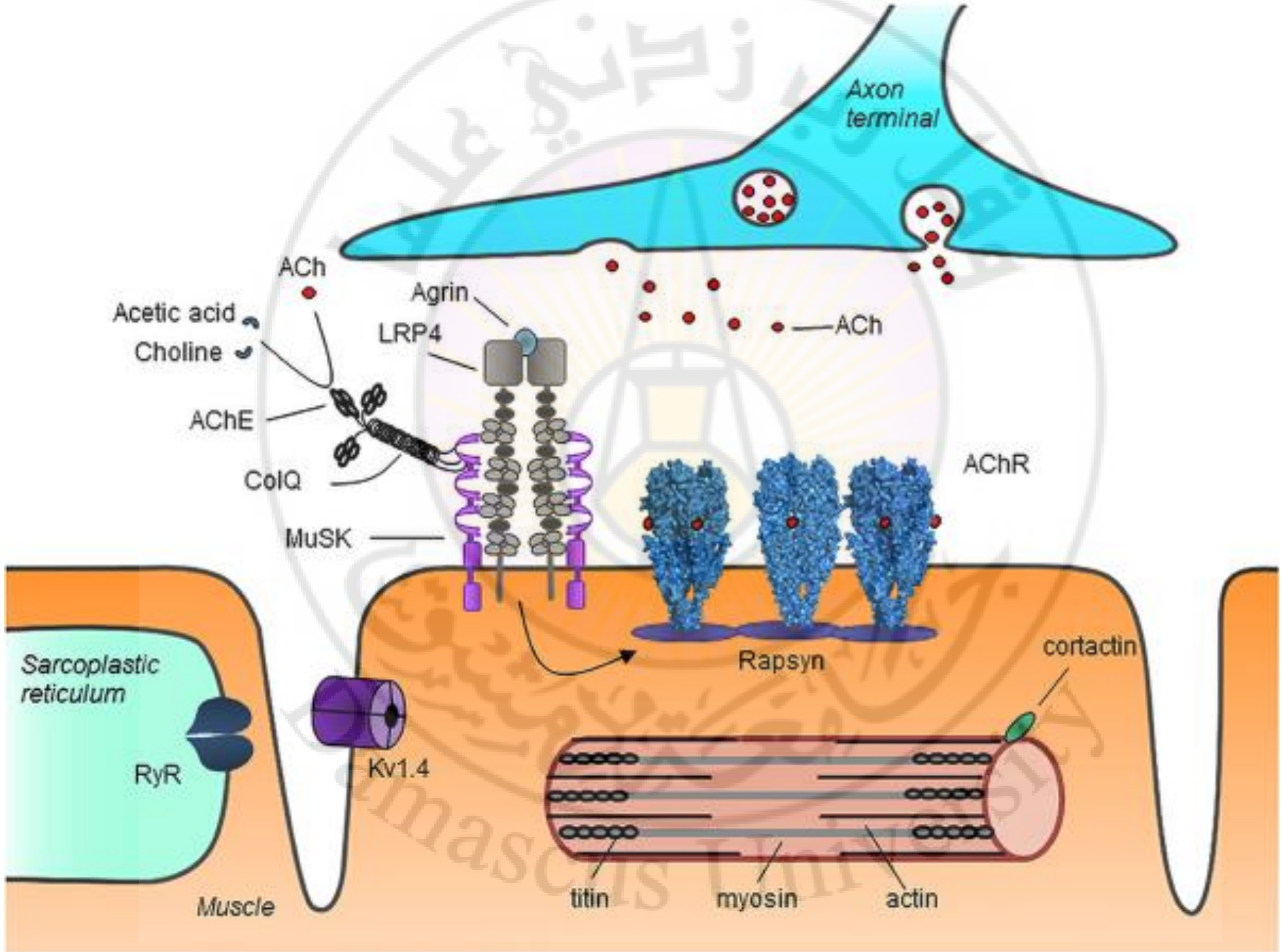

Normal
Axon
Vesicle
Mitochondrion
Release site
Nerve terminal
Acetylcholine receptors
Muscle
Acetylcholinesterase

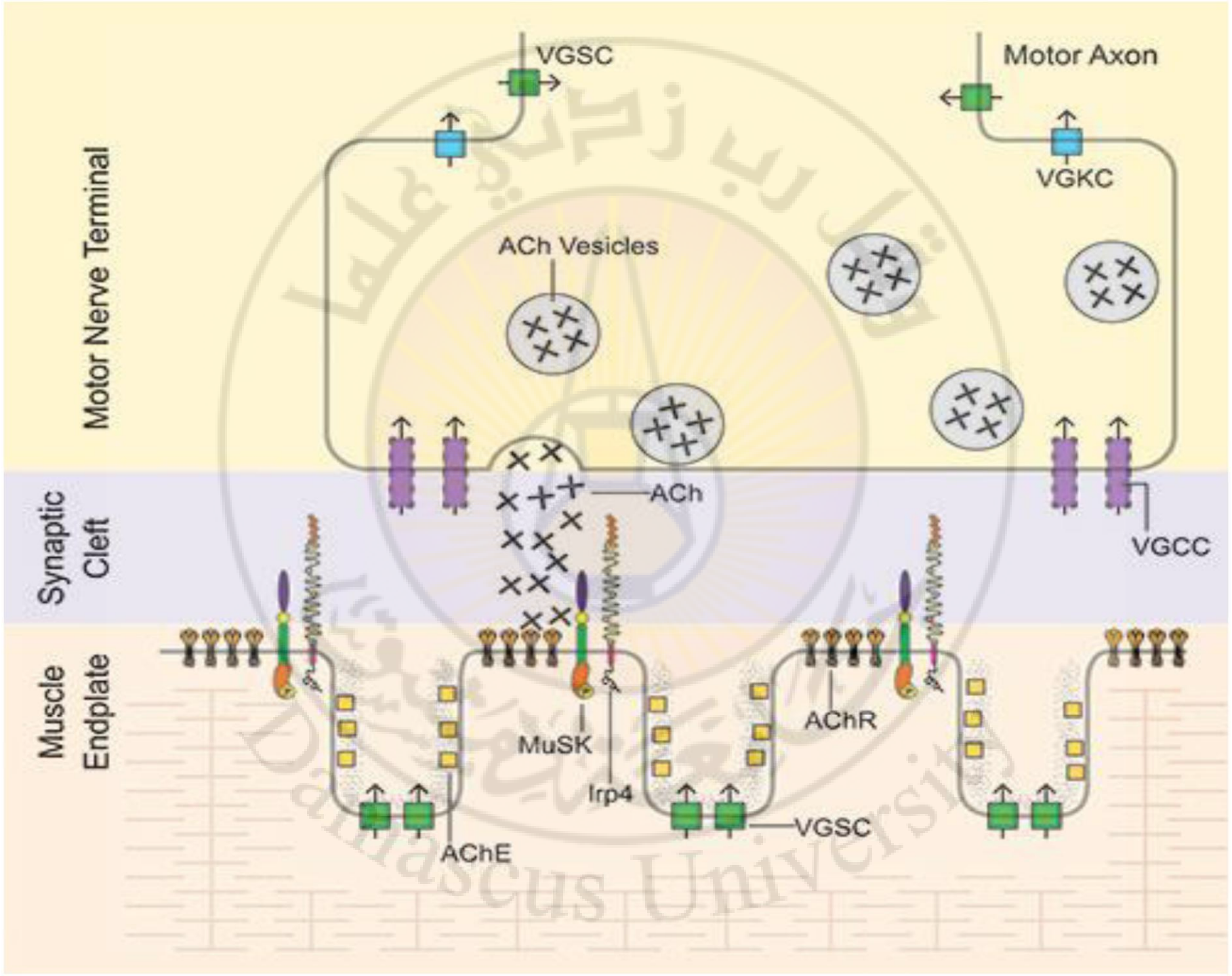
Myasthenia gravis




Nerve terminal
Agrin
Synaptic vesicle
Rspo2
Synaptic cleft
Agrin
Rspo2
ACh
Lrp4
MuSK
P
P
Lgr5
AChR cluster
DVL
Muscle

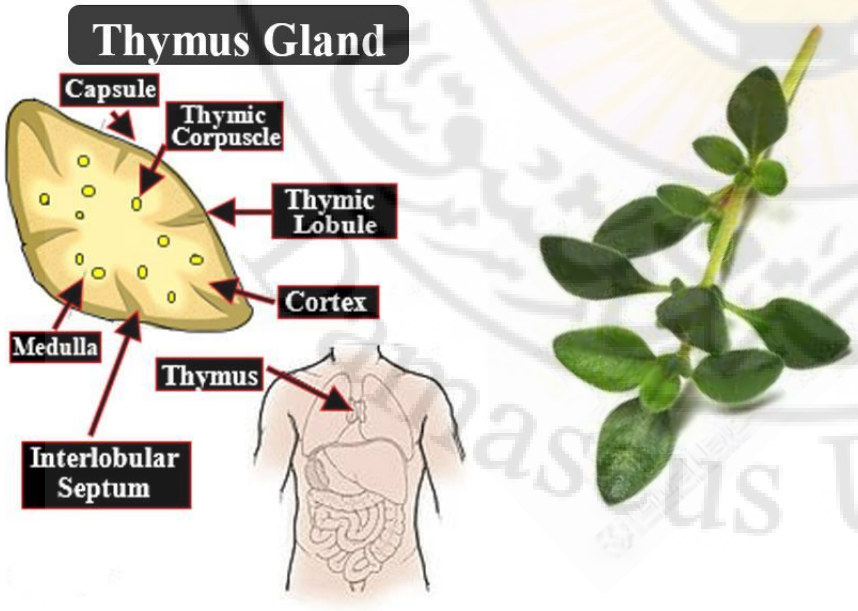

choline
+
acetyl CoA
ChAT
nerve terminal
ACh
vesicles
AChE
AChR
LRP4
Agrin
MuSK
DOK7
Rapsyn
muscle
VGNa+C

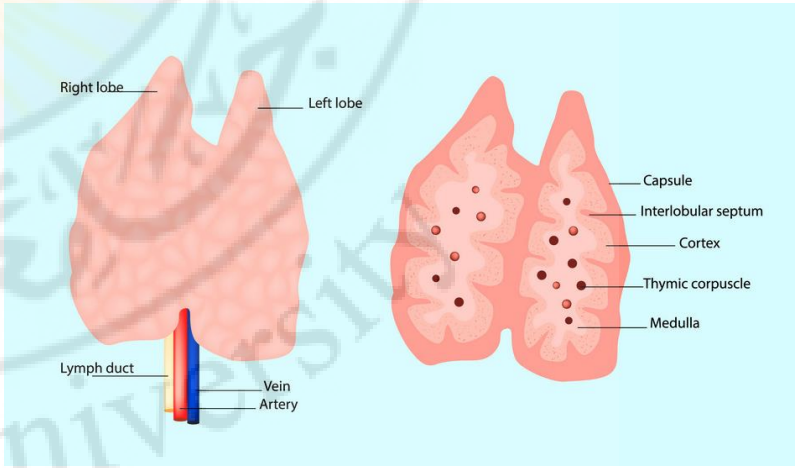

Axon terminal
ACh
Acetic acid
Choline
Agrin
LRP4
ACh
AChE
ColQ
MuSK
AChR
Rapsyn
cortactin
Sarcoplastic reticulum
RyR
Kv1.4
Muscle
titin
myosin
actin

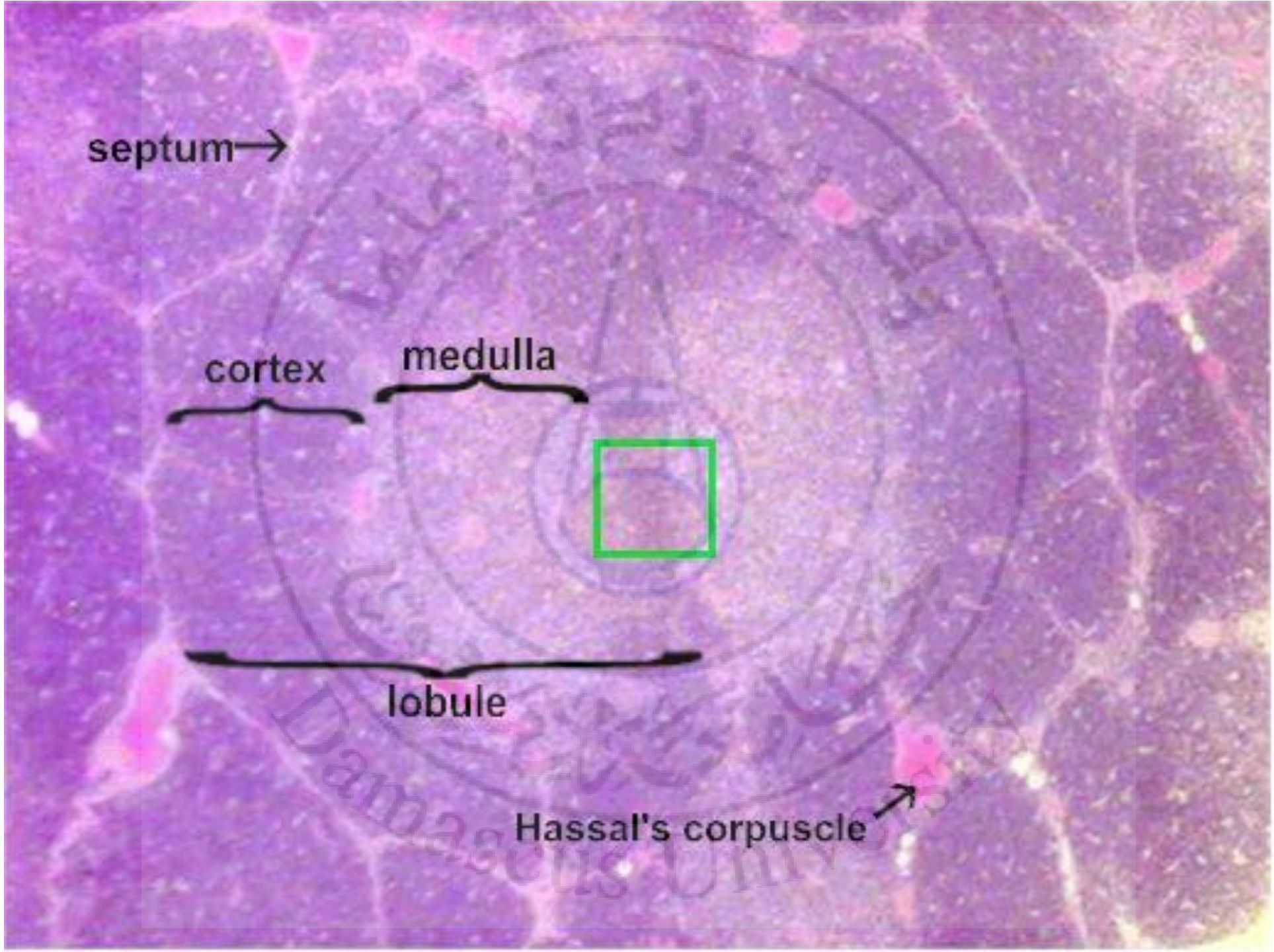

Motor Nerve Terminal
Synaptic Cleft
Muscle Endplate
VGSC
Motor Axon
VGKC
ACh Vesicles
ACh
VGCC
MuSK
Irp4
AChR
VGSC
AChE

The Thymus :

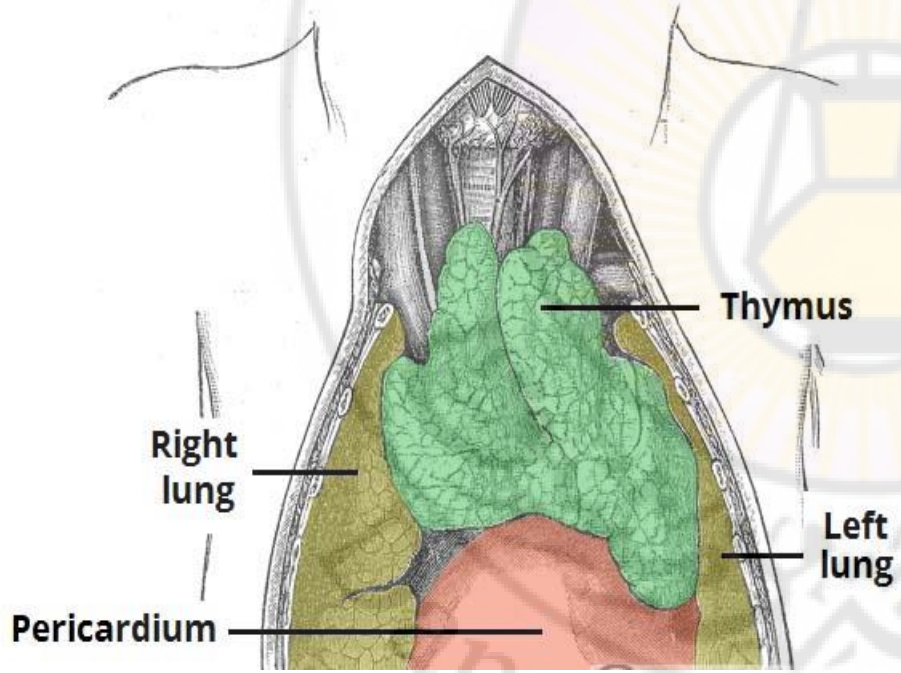
The thymus is a lymphoid gland comprised of two identically sized lobes, located behind the sternum (breastbone) but in front of the heart. It derives its name from a resemblance it bears to the bud of the thyme plant (thymus in Latin).



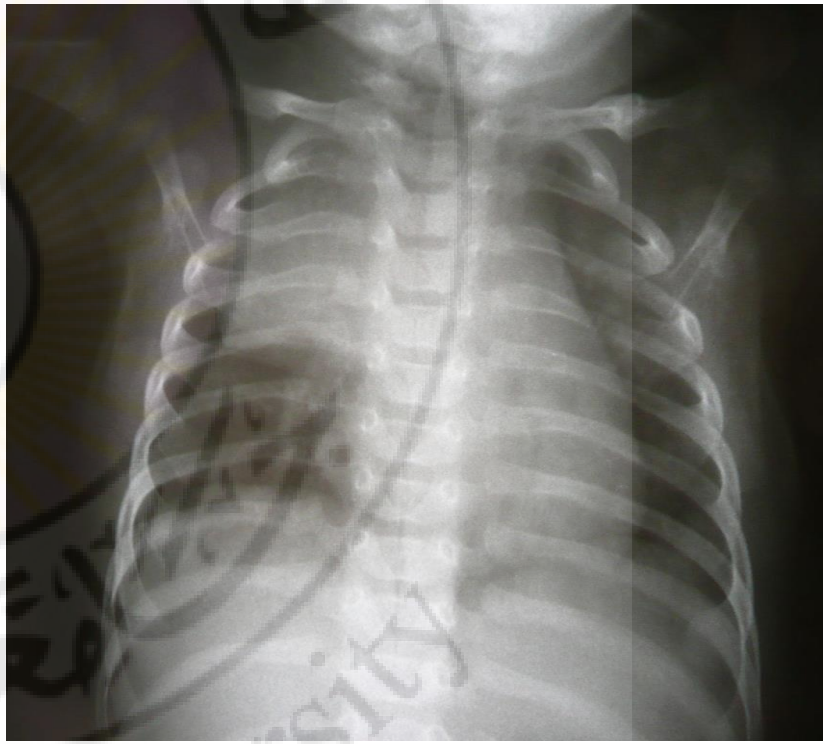



septum
cortex
medulla
lobule
Hassal's corpuscle

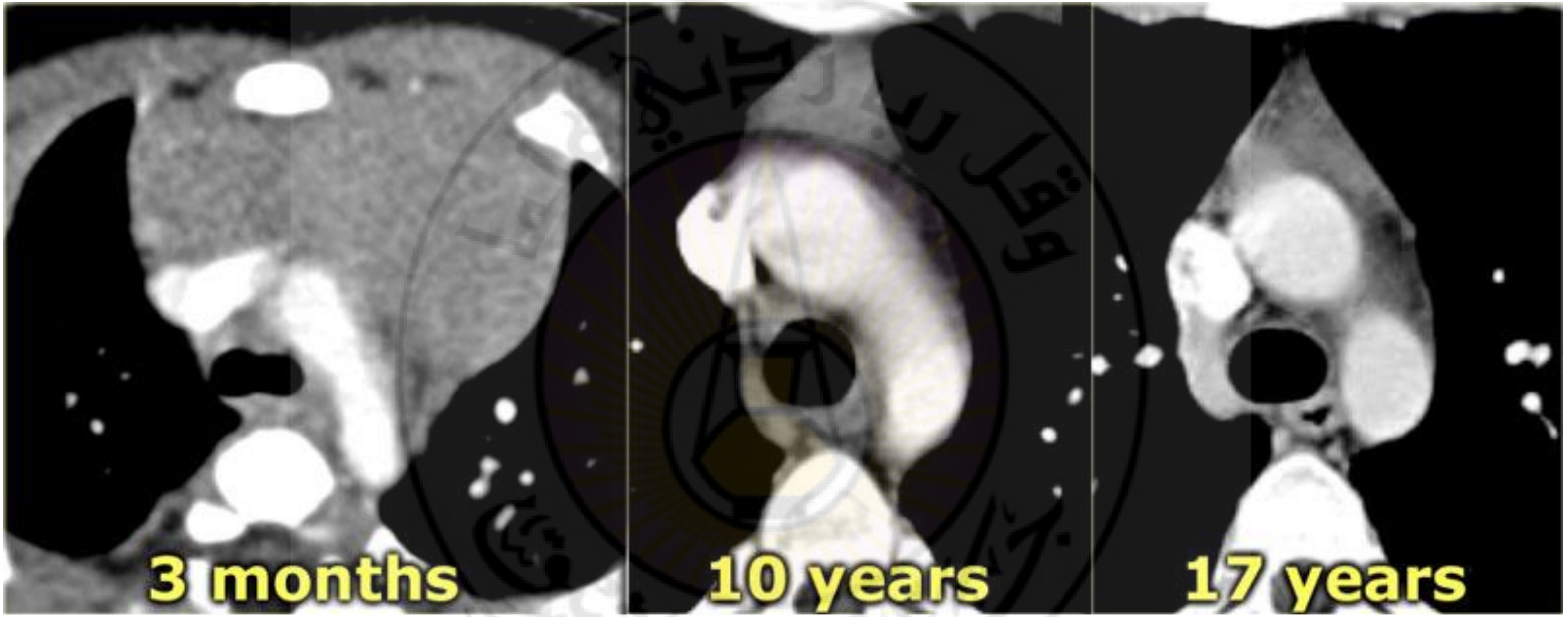
At puberty, the thymus reaches the height of its use, becoming its largest. After this age, the size of the thymus declines as the lymphoid tissue disappears and fat and fibrous tissue appears.



Thymus of a fetus



On chest X-ray, the thymus appears as a radiodense (brighter in this image) mass by the upper lobe of the child's right (left in image) lung.

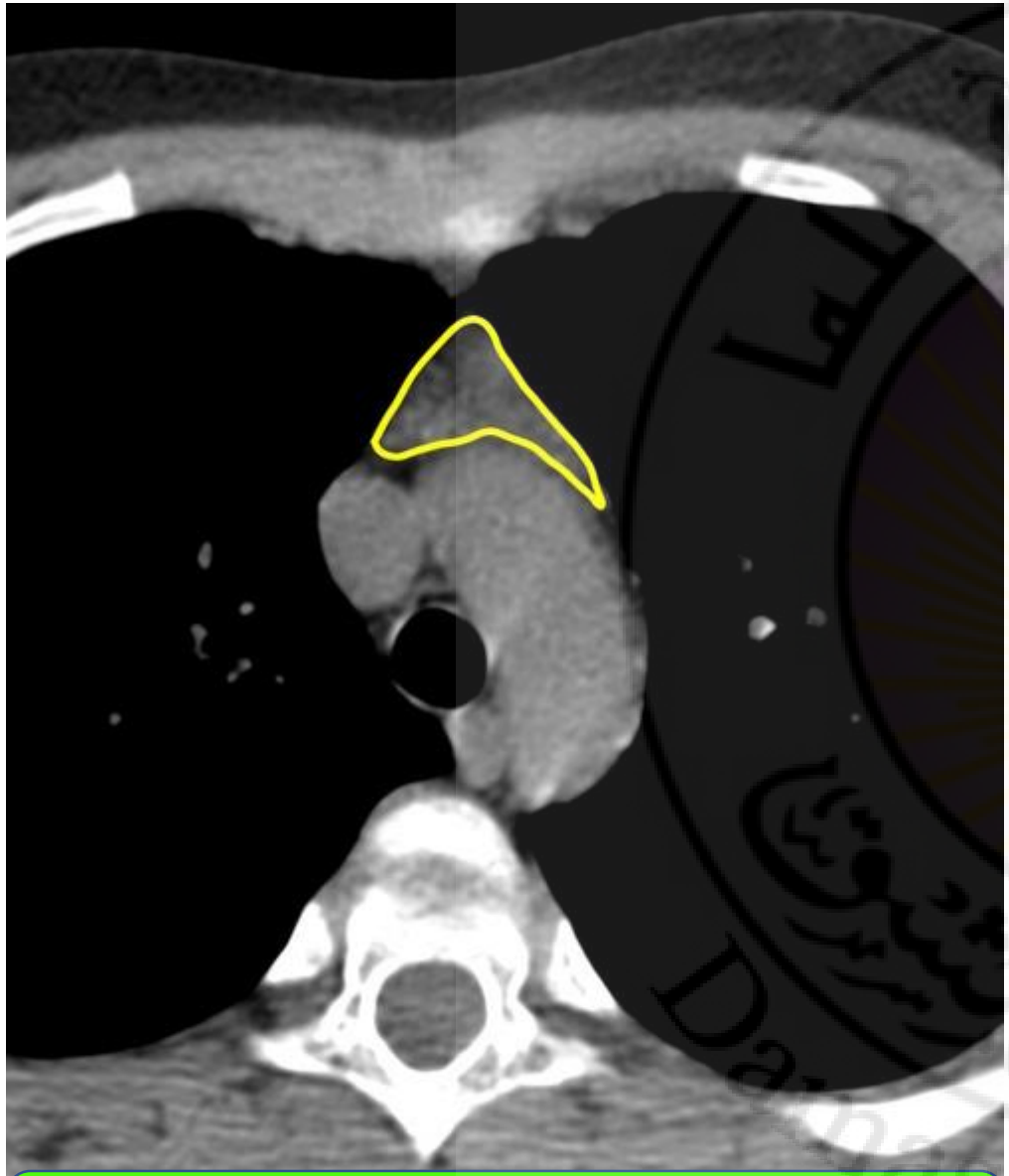


Thymus

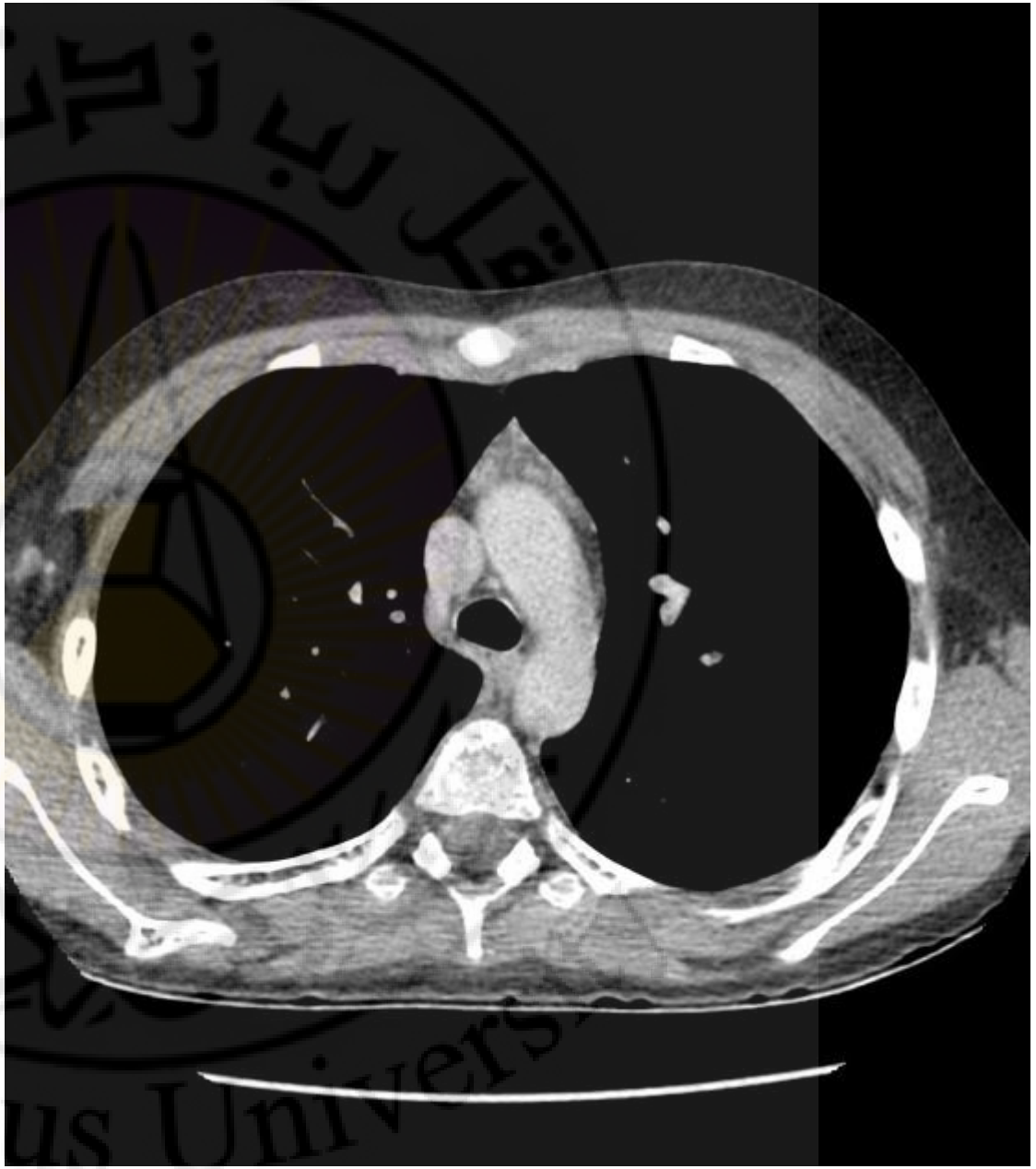
In infants and young children (In older children, the thymus gradually assumes a triangular or arrowhead configuration with straight or concave margins.

By 15 years of age it is triangular in nearly all individuals.

Marked lobularity of the thymus is always abnormal.



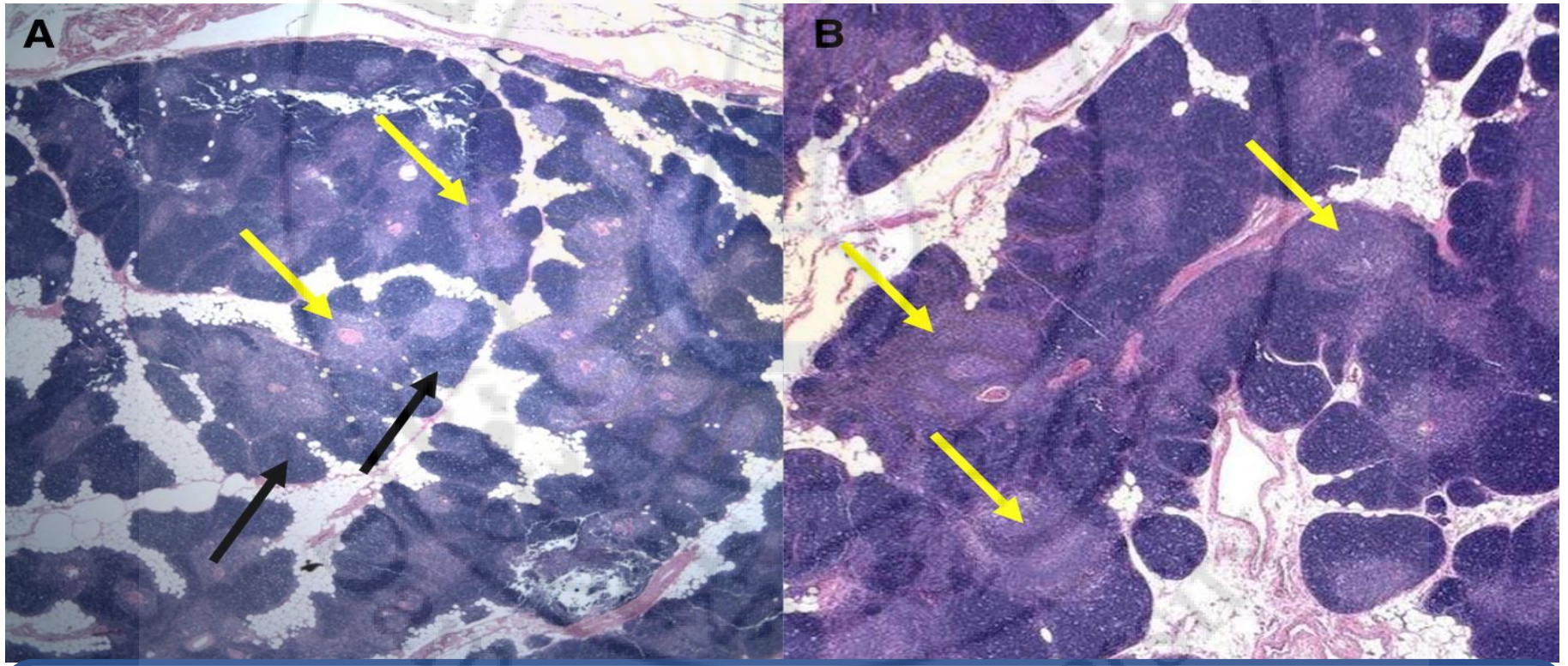
Yellow line delineating the two asymmetric lobes of the thymus.



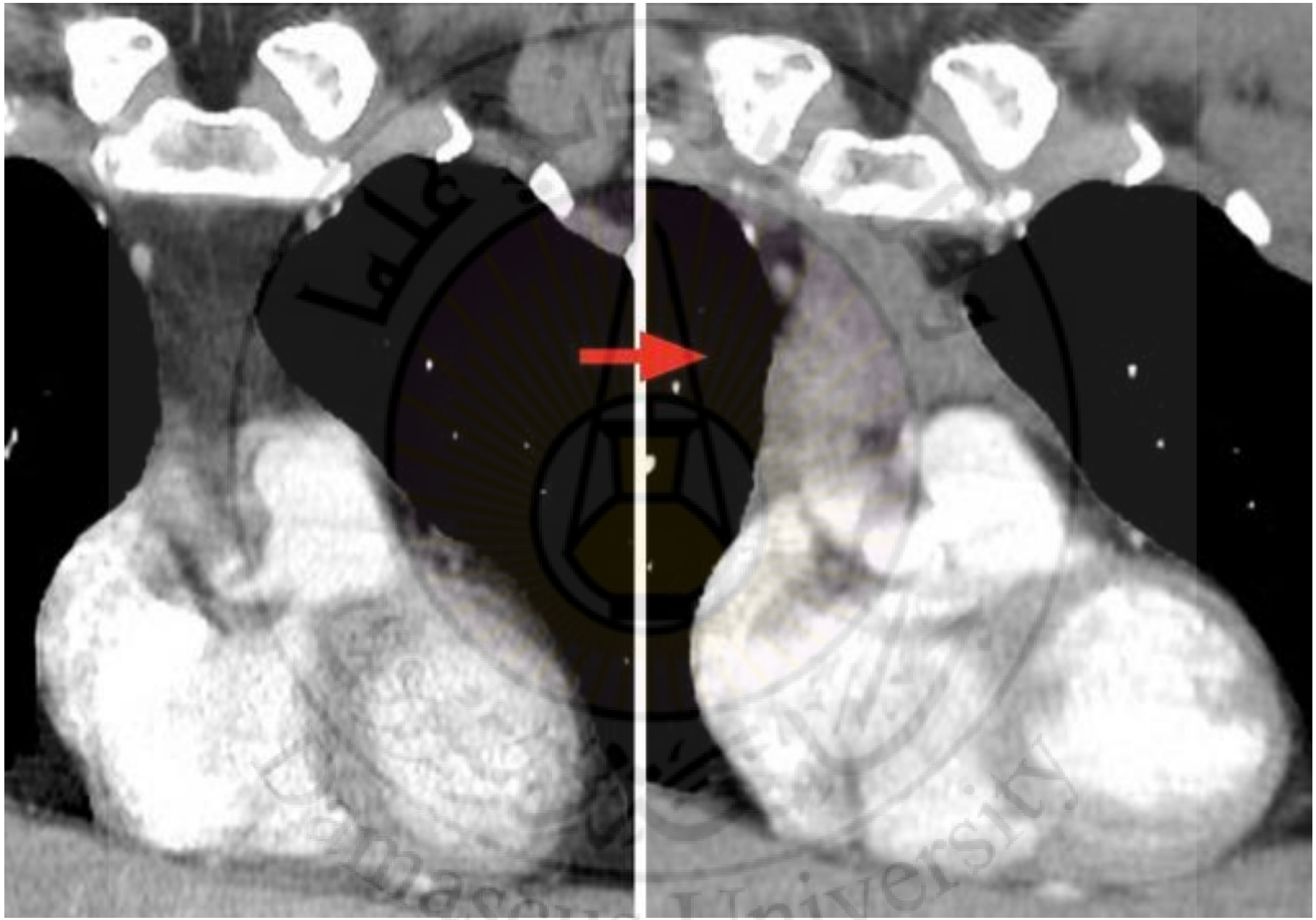
Thymic Hyperplasia

True thymic hyperplasia, with increased numbers of thymic epithelial cells (black arrows) and lymphoid germinal centers (yellow arrows)

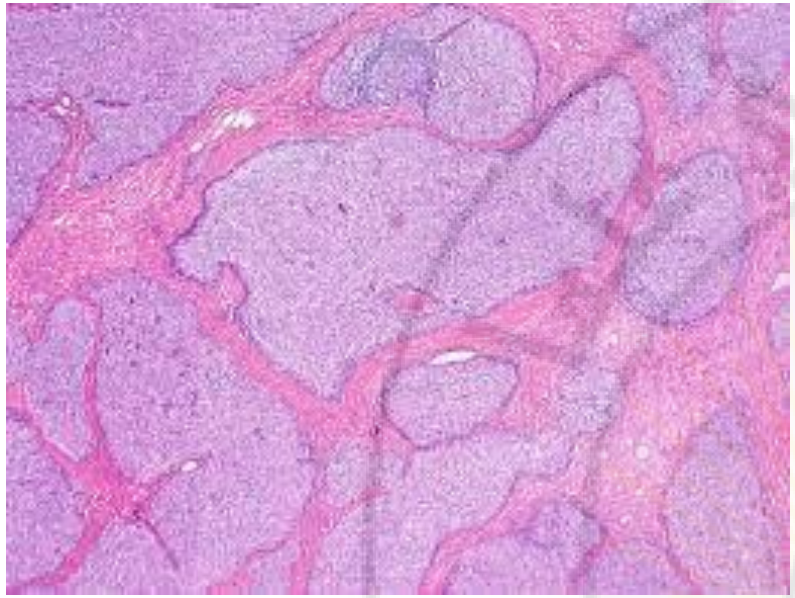
Lymphoid follicular hyperplasia, with enlarged germinal centers present throughout (yellow arrows)

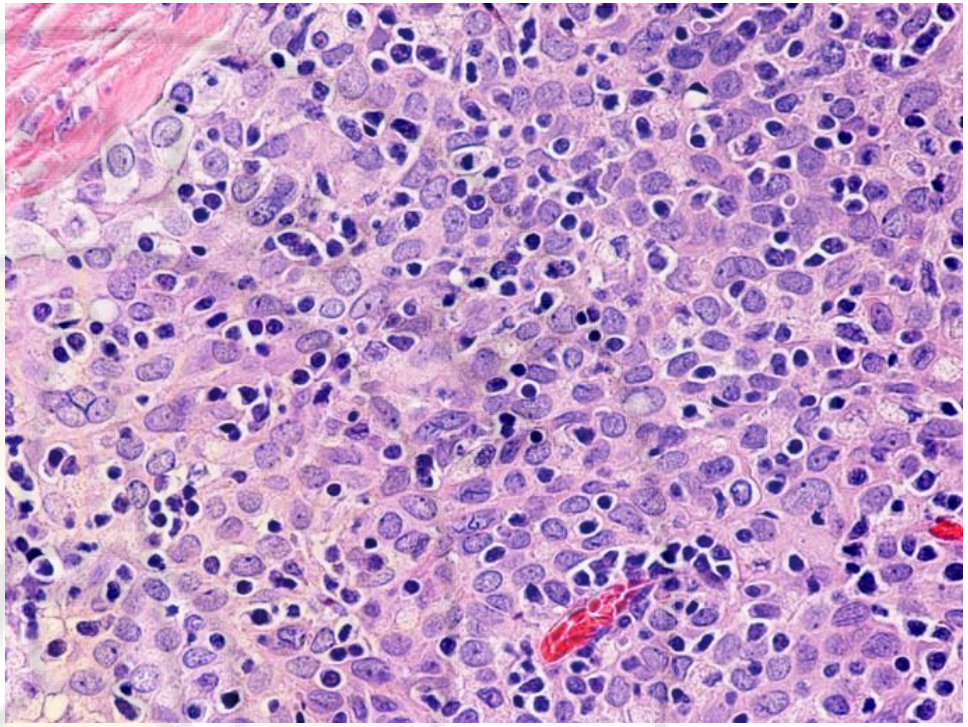


The mechanism of hyperplasia is believed to be initial depletion of lymphocytes from the cortical portion of the gland due to high serum levels of glucocorticoids, followed by repopulation of the cortical lymphocytes when the cortisone levels return to normal.



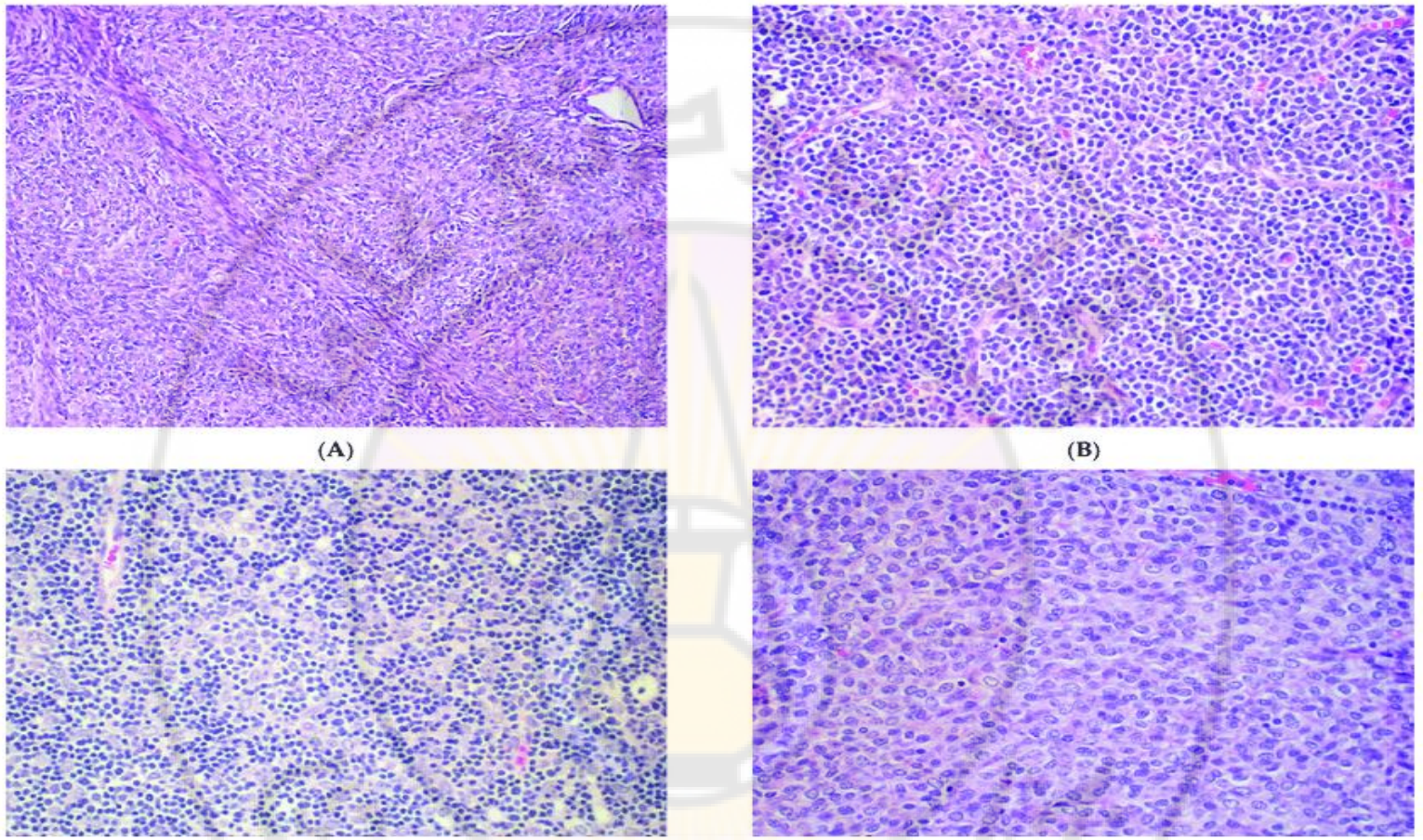
These 2 entities are indistinguishable from one another at imaging.



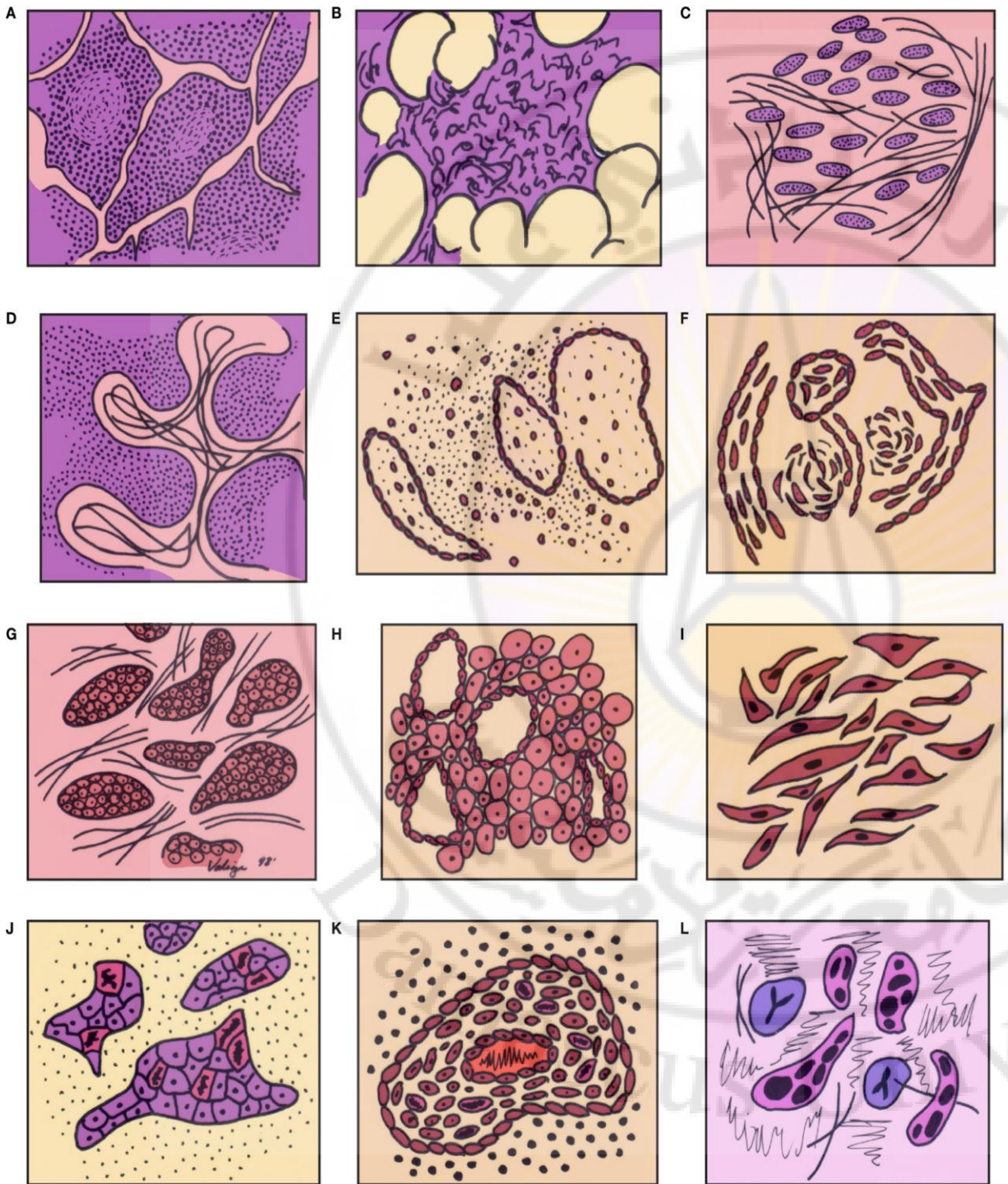


Three principal histological types of thymoma, depending on the appearance of the cells by microscopy:

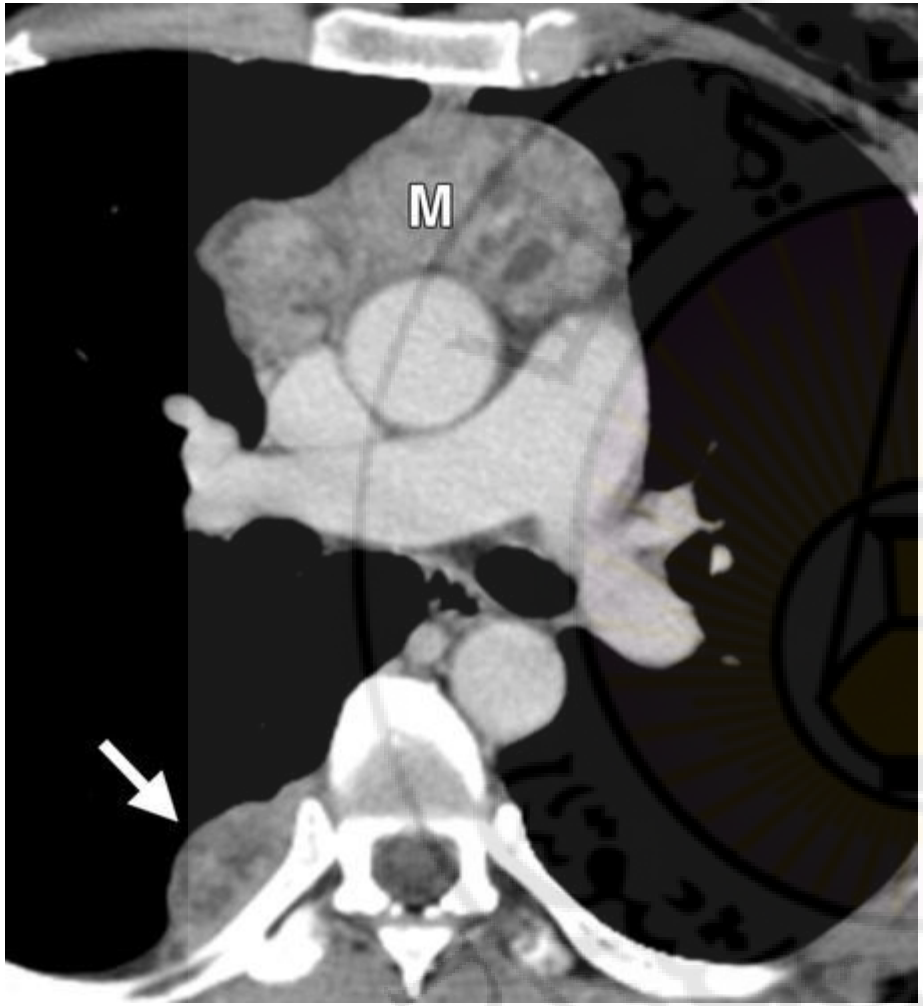
Type A if the epithelial cells have an oval or fusiform shape (less lymphocyte count);
Type B if they have an epithelioid shape
(Type B has three subtypes: B1 (lymphocyte-rich), B2 (cortical) and B3 (epithelial)).
Type AB if the tumor contains a combination of both cell types.

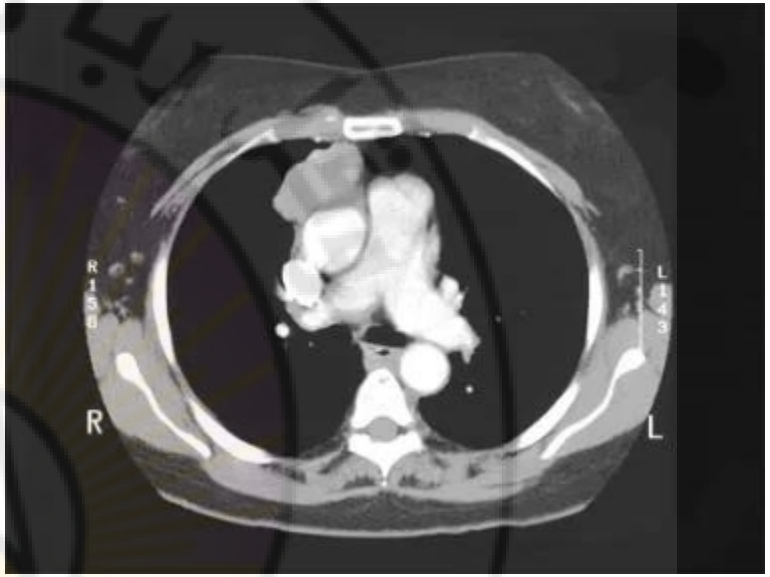


Histological subtypes of thymoma. (A) Type A thymoma with spindle epithelial cells. (B) Type B1 thymoma with rare epithelial cells and abundant lymphocytes. (C) Type B2 thymoma with
Histological subtypes of thymoma. (A) Type A thymoma with spindle epithelial cells. (B) Type B1 thymoma with rare epithelial cells and abundant lymphocytes. (C) Type B2 thymoma with epithelial islands admixed with lymphocytes. (D) Type B3 thymoma with round to ovoid epithelial cells and rare lymphocytes. All images show H&E stains, 20× objective.

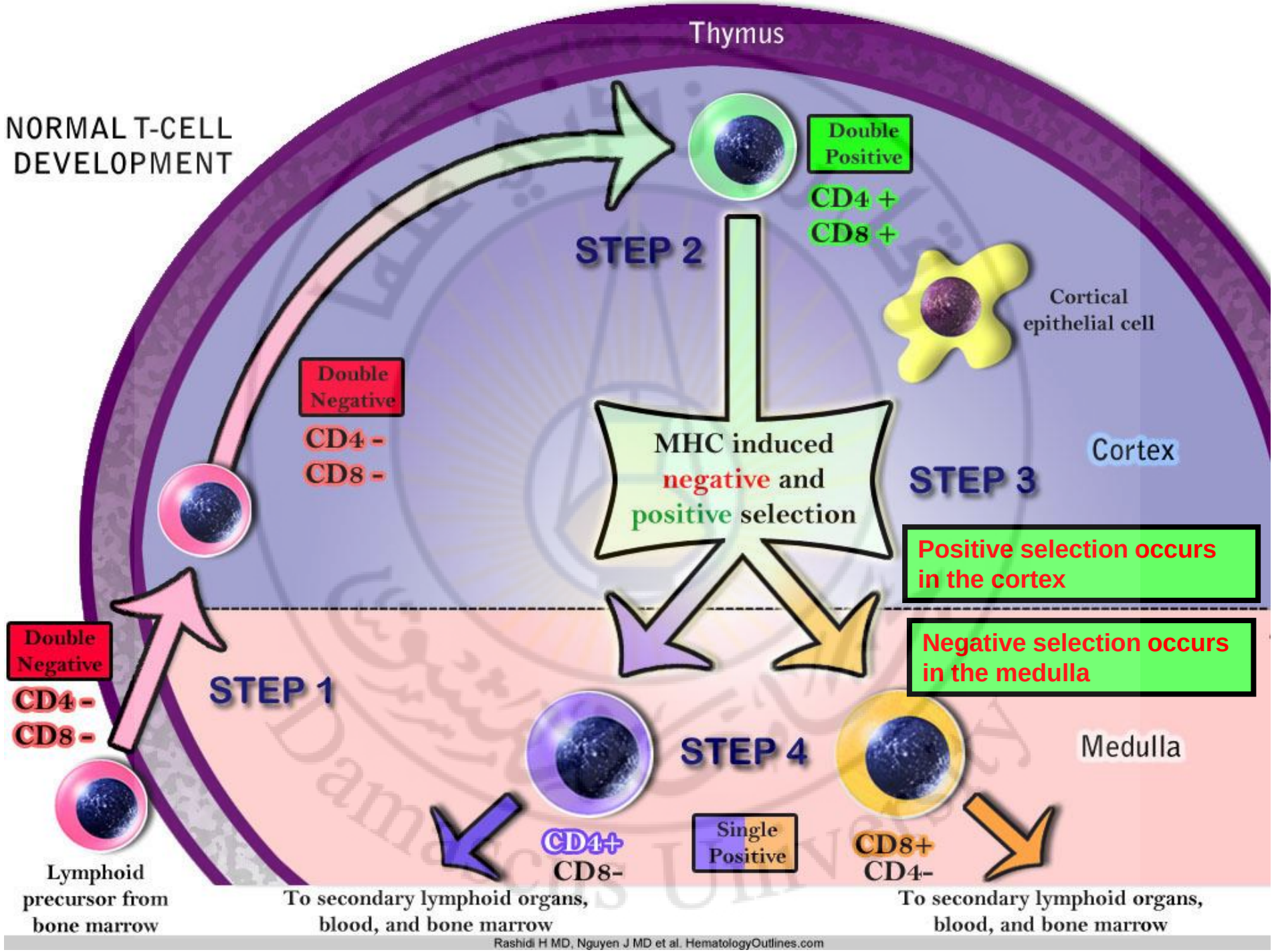


(A) thymus in a child, (B) thymus in the adult, (C) thymus with involutional changes, (D) thymoma (lymphocyte rich – WHO type B1), (E) Thymoma (mixed cellularity – WHO type B2), (F) Spindle cell thymoma (WHO type A), (G) atypical thymoma – preservation of organotypical features, (H) atypical thymoma (perivascular spaces), (I) Atypical spindle cell thymoma, (J) thymic carcinoma – loss of organotypical features, (K) thymic carcinoma – inflammatory reaction, (L) thymic carcinoma – cellular atypia and mitotic activity in epithelial



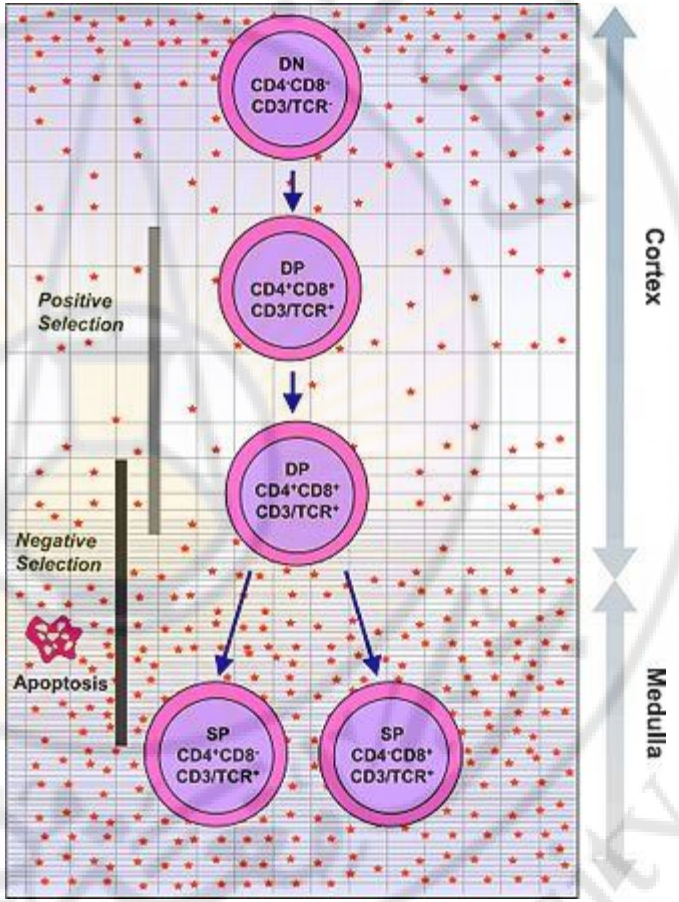


CT scan clearly illustrates mass in right anterolateral mediastinum.

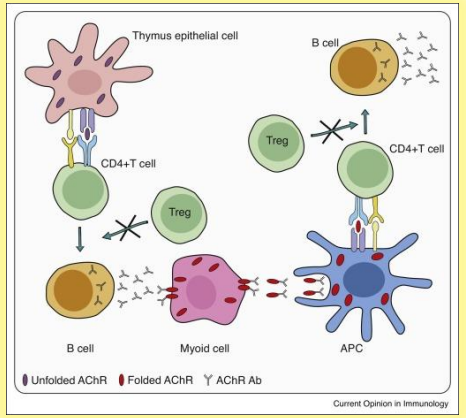

NORMAL T-CELL DEVELOPMENT
Thymus
Double Positive
CD4 +
CD8 +
STEP 2
Cortical epithelial cell
Double Negative
CD4 -
CD8 -
MHC induced negative and positive selection
STEP 3
Cortex
Positive selection occurs in the cortex
Negative selection occurs in the medulla
Double Negative
CD4 -
CD8 -
STEP 1
STEP 4
Medulla
CD4+
CD8-
Single Positive
CD8+
CD4-
Lymphoid precursor from bone marrow
To secondary lymphoid organs, blood, and bone marrow
To secondary lymphoid organs, blood, and bone marrow
Rashidi H MD, Nguyen J MD et al. HematologyOutlines.com

In the thymus they undergo a process of maturation, which involves ensuring the cells react against antigens ("positive selection"), but that they do not react against antigens found on body tissue ("negative selection")

The survival and nature of the T cell then depends on its interaction with surrounding thymic epithelial cells. Here, the T cell receptor interacts with the MHC molecules on the surface of epithelial cells. A T cell with a receptor that doesn't react, or reacts weakly will die by apoptosis. A T cell that does react will survive and proliferate.
A mature T cell expresses only CD4 or CD8, but not both

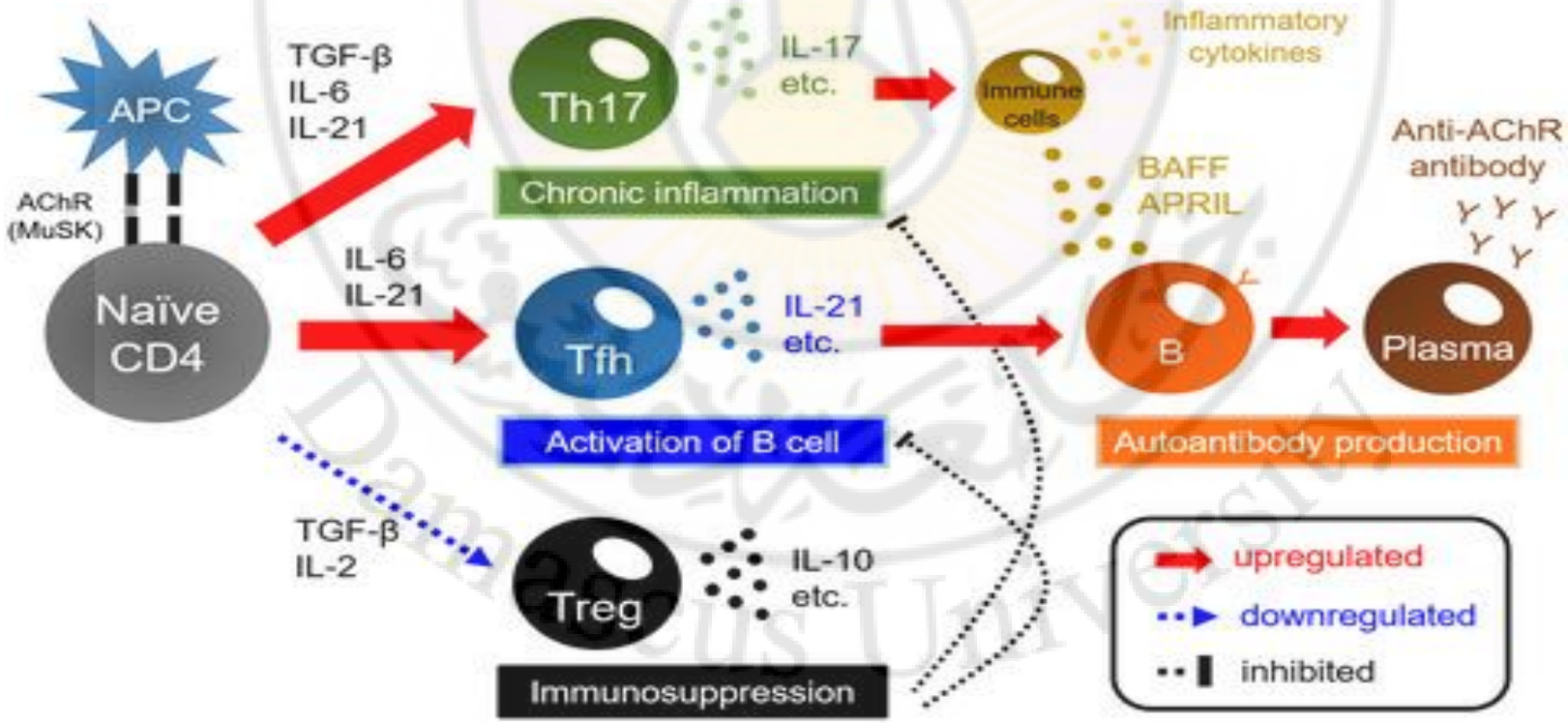


Positive selection occurs in the cortex and negative selection occurs in the medulla of the thymus



Epithelial cells in the medulla and dendritic cells in the thymus express major proteins from elsewhere in the body

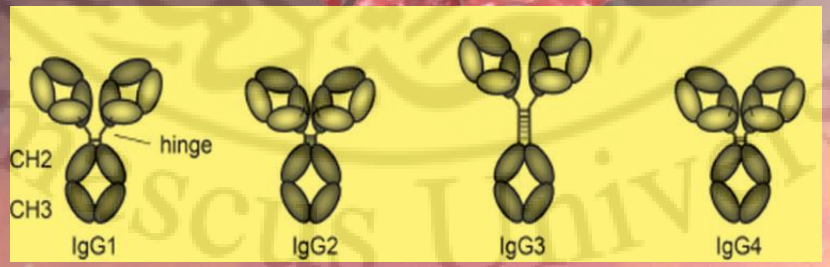
The normal immune system weeds out autoreactive T cells early and these are destroyed in the thymus by the process called central tolerance. Autoreactive T cells that escape this process or arise de novo, are kept in check in the peripheral circulation by a subset of CD4+ cells called Treg cells that bring about apoptosis, anergy or suppression of autoreactive cells . These T reg cells which are outsourced from the thymus gland are crucial in maintaining immune tolerance and are found to be functionally deficient in MG

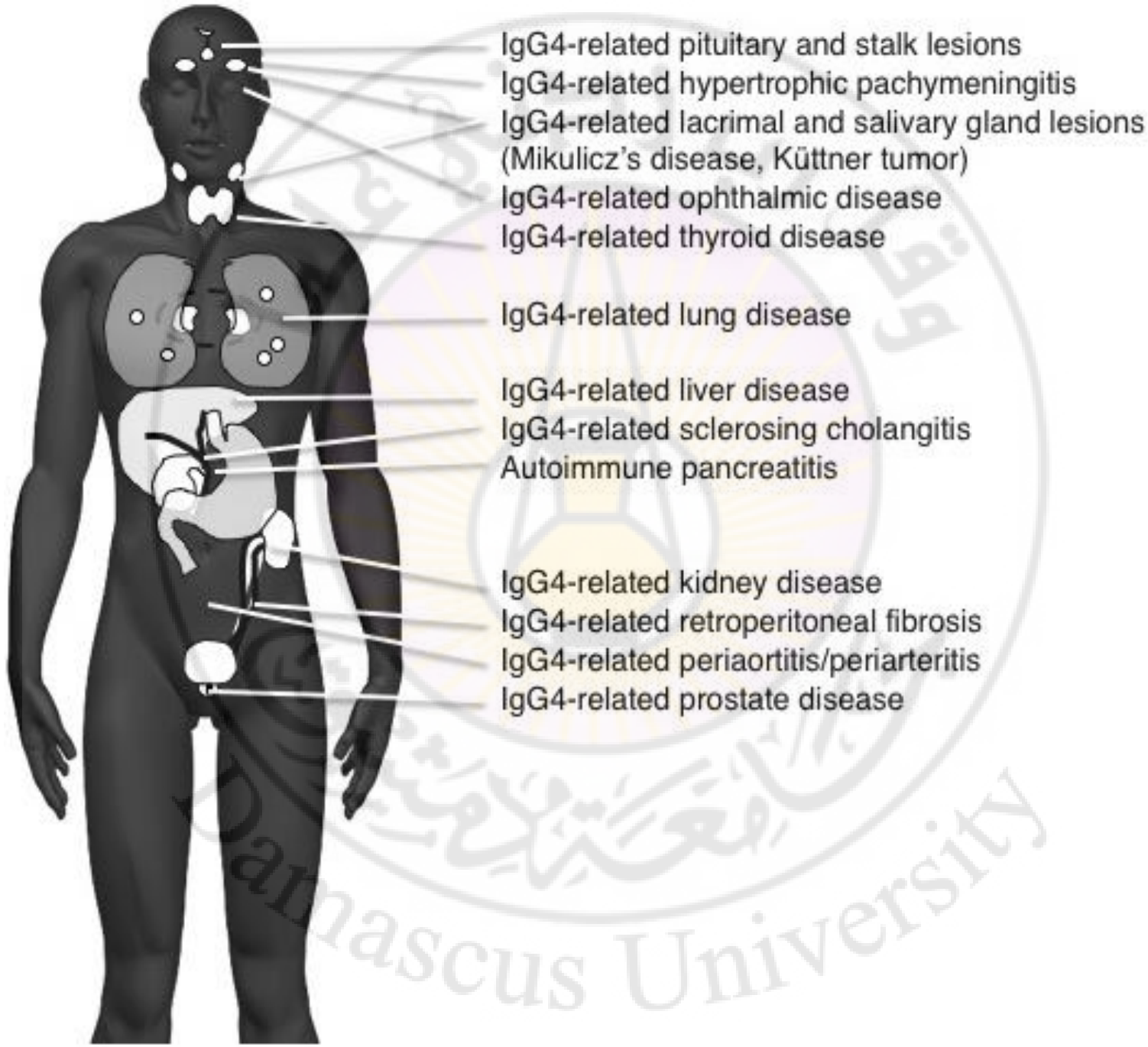


Complex interplay between CD4+ T cells and B cells

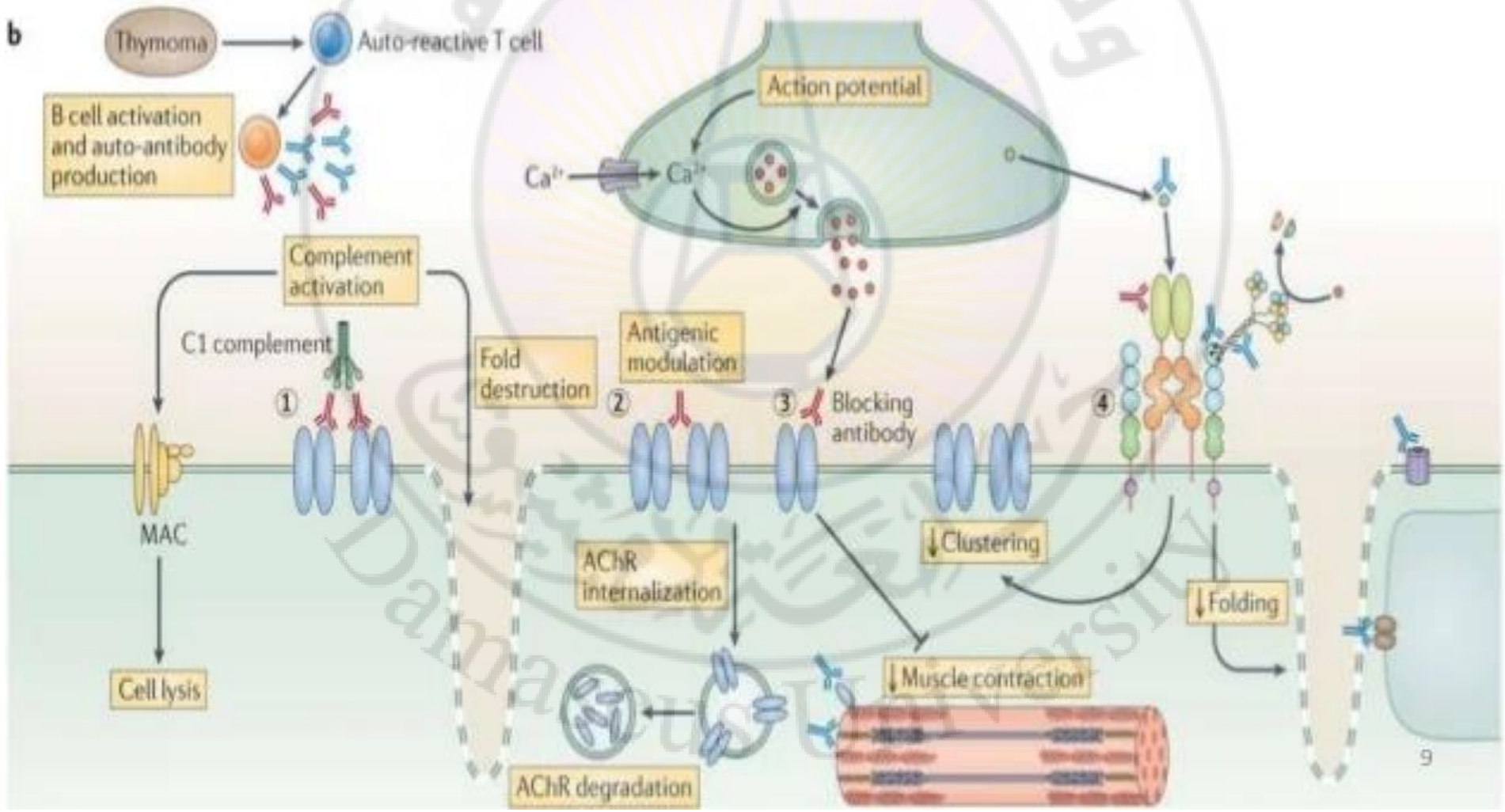
The AChR antibodies are predominantly IgG1 and IgG3 subclasses and lead to loss of AChRs by two main mechanisms; mainly complement activation, cross-linking and internalization of AChRs

MuSK autoantibodies are predominantly of the IgG4 subtype and impair agrin signaling by disrupting the interaction of MuSK with the low density lipoprotein receptor-related protein-4 (LRP4)




IgG4-related pituitary and stalk lesions
IgG4-related hypertrophic pachymeningitis
IgG4-related lacrimal and salivary gland lesions
(Mikulicz's disease, Küttner tumor)
IgG4-related ophthalmic disease
IgG4-related thyroid disease
IgG4-related lung disease
IgG4-related liver disease
IgG4-related sclerosing cholangitis
Autoimmune pancreatitis
IgG4-related kidney disease
IgG4-related retroperitoneal fibrosis
IgG4-related periaortitis/periarteritis
IgG4-related prostate disease

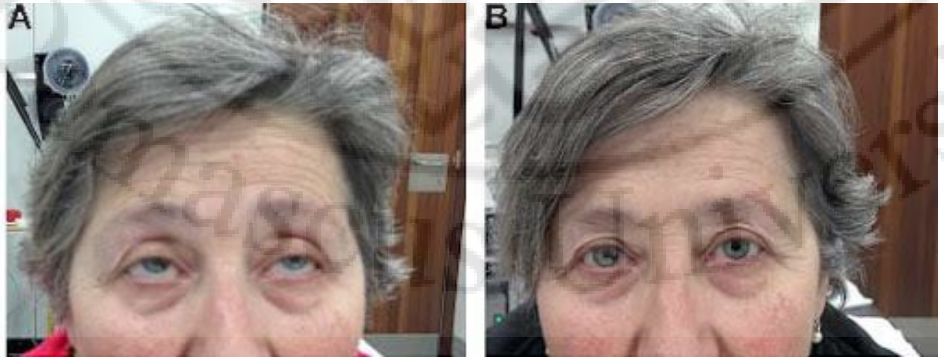
Pathophysiology



A. Starting with the bedside tests:

The edrophonium test :

- **This test is based on the idea that by preventing the degradation of Ach and increasing its concentration at the NMJ, the patient's symptoms will consequently improve .**
- **As a result , Edrophonium - a short-acting AChE inhibitor – can dramatically improve the muscle weakness of patients with M.G.**

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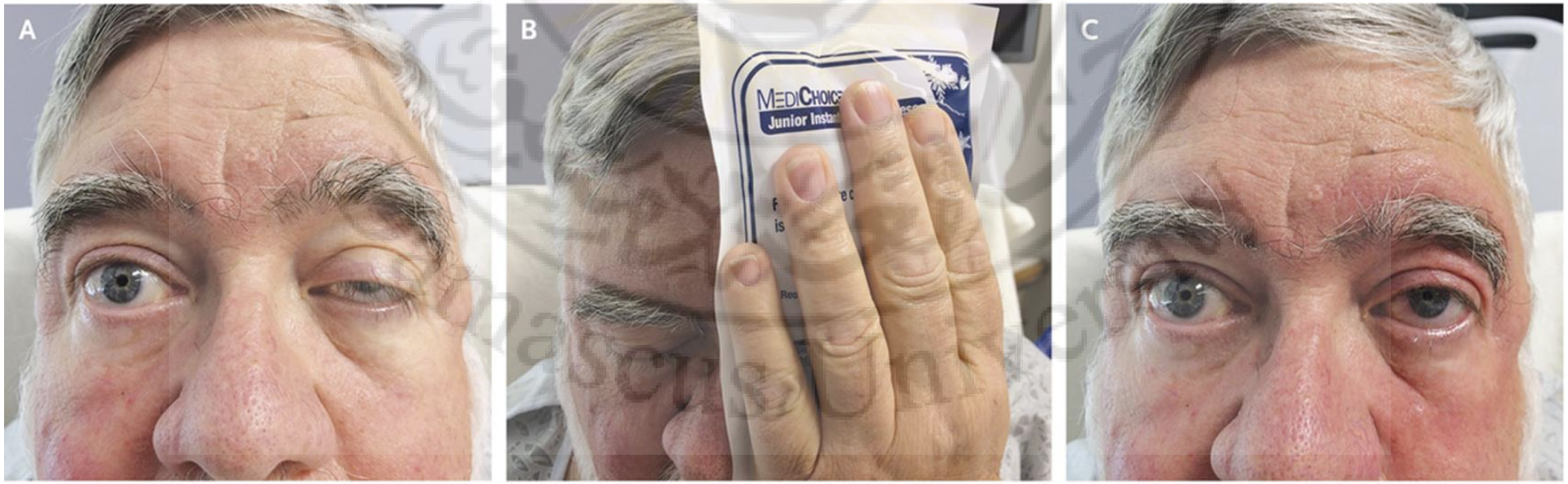
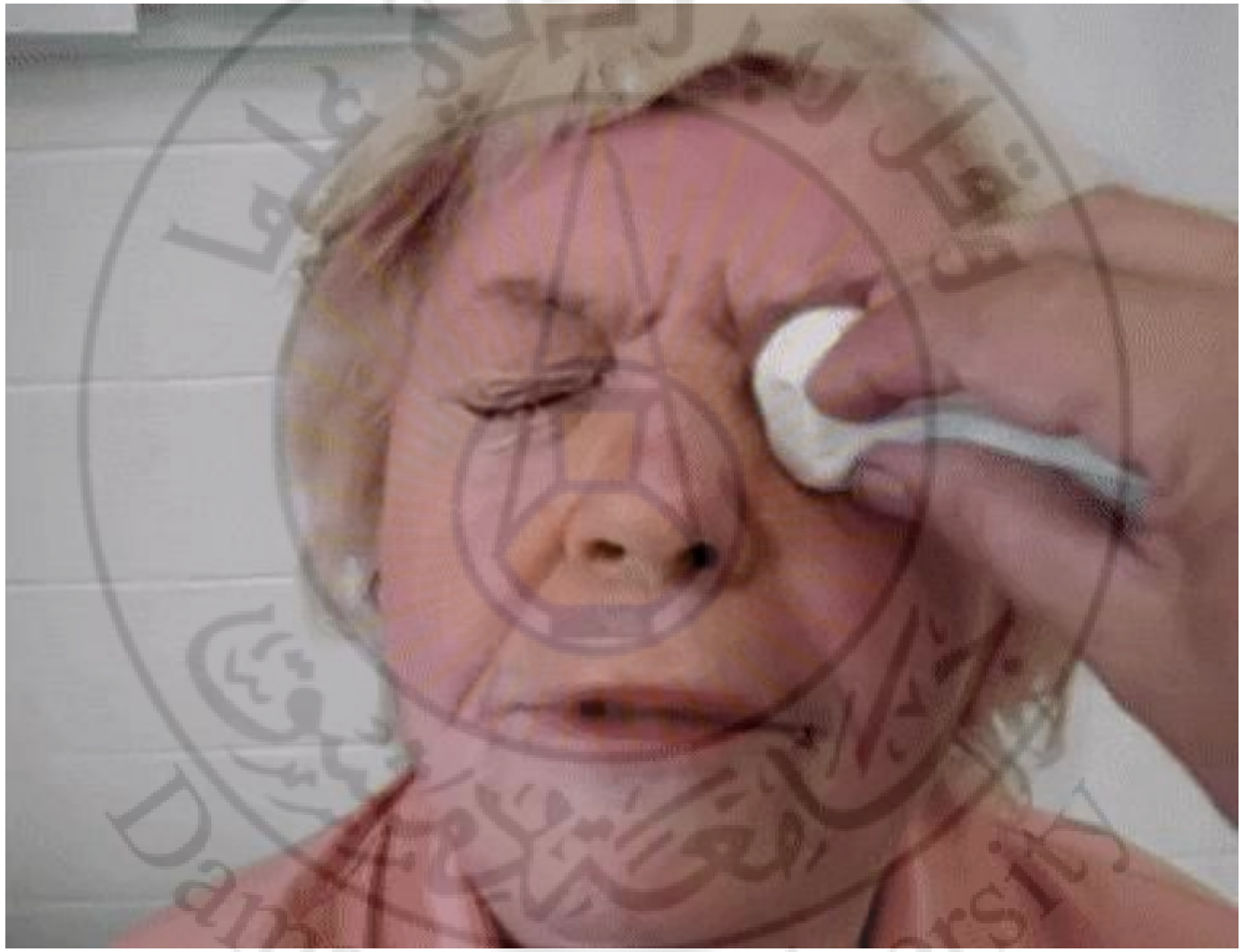
The ice pack test :

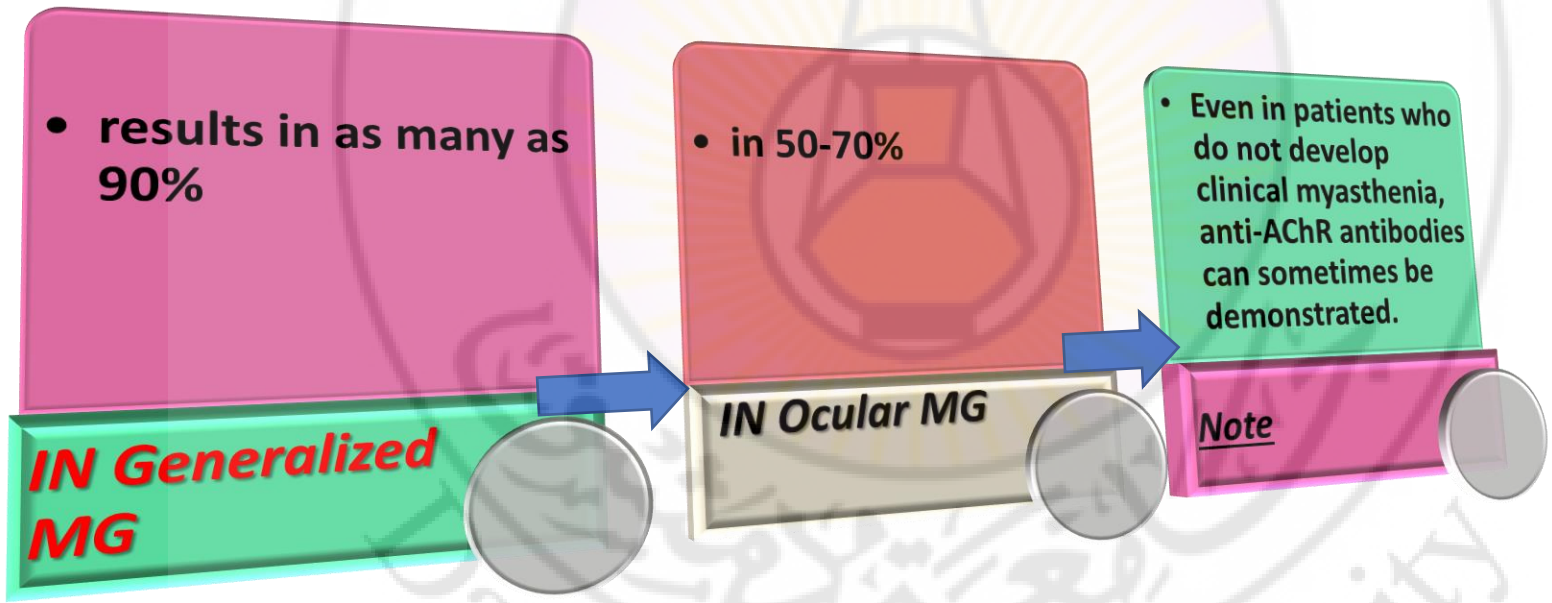
1. helps evaluate the patient's improvement
2. the point is that cooling may improve neuromuscular transmission



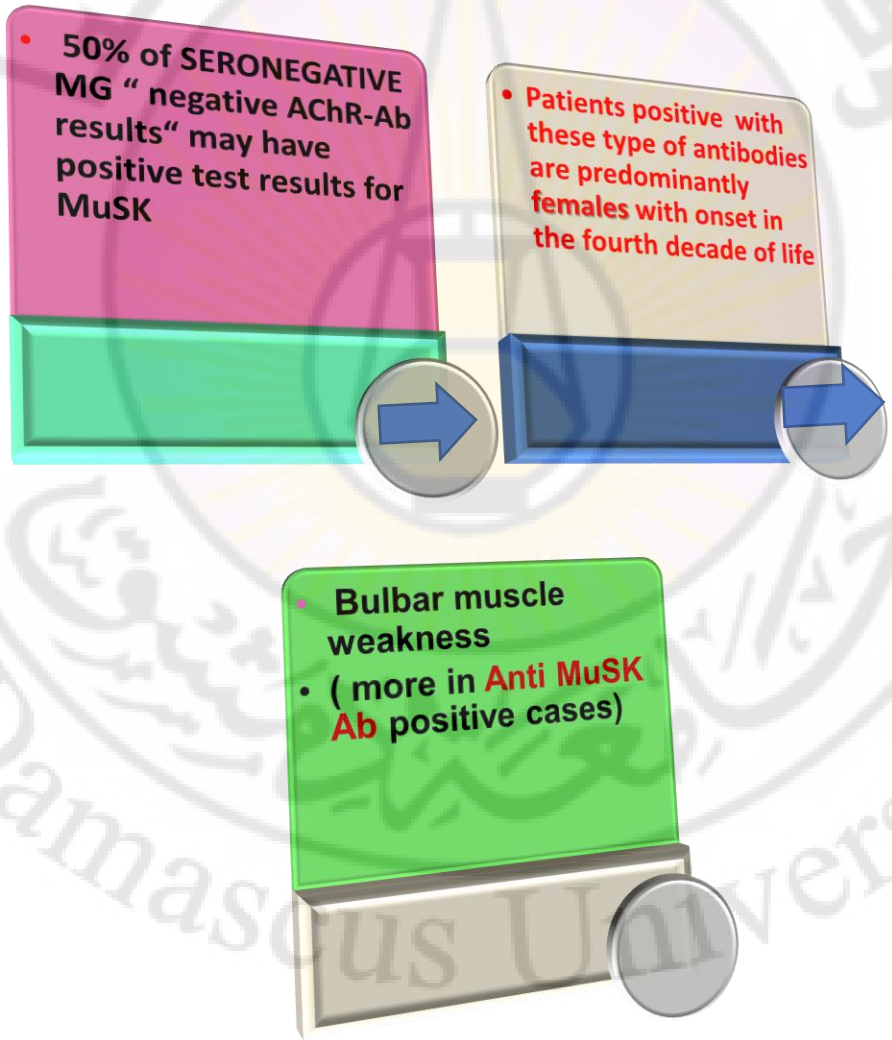


B. Laboratory tests :

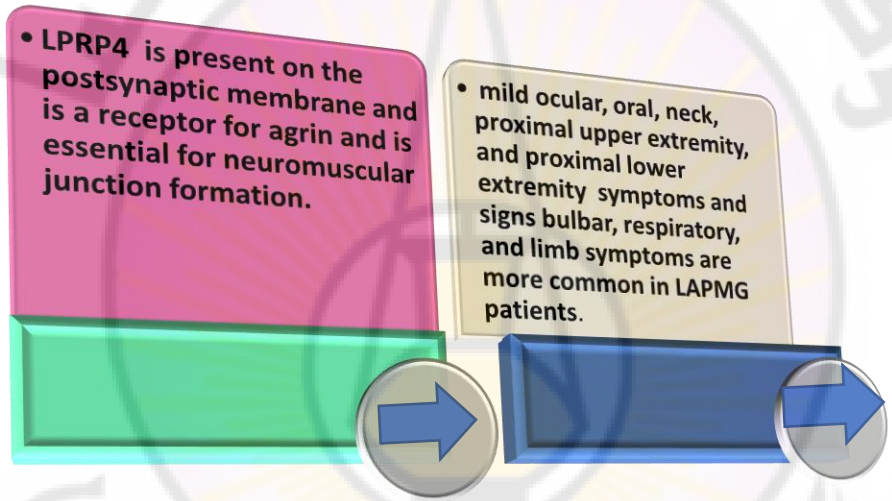
Anti –acytelcholine receptor antibody (AChR-Ab)

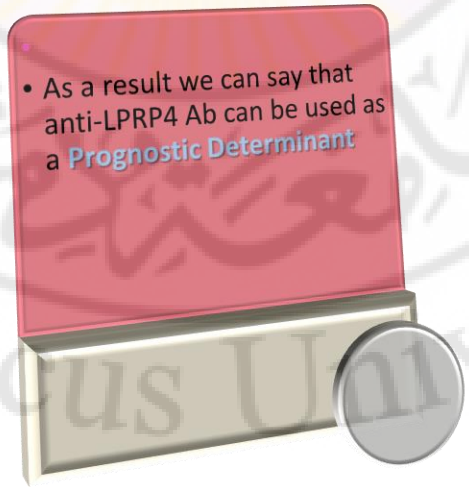


Anti-MuSK Antibodies



Anti-Lipoprotein-related protein 4 (LPRP) antibody and Agrin





REMEMBER :

50% Patients with NEGATIVE AChR-Ab

↓

POSITIVE Anti-MuSK Ab

2-27% Patients with NEGATIVE AChR-Ab + MuSK-Ab

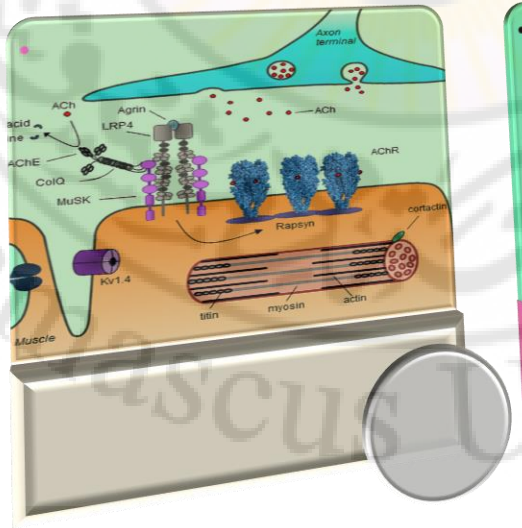
↓

POSITIVE anti- LPRP4 Ab and Agrin

Antistriational Antibodies

- Serum from some patients with MG possesses antibodies that bind in a cross-striational pattern to skeletal and heart muscle tissue sections. These antibodies react with epitopes on the muscle protein titin and ryanodine receptors (RyR).

- Almost all MG patients with THYMOMA

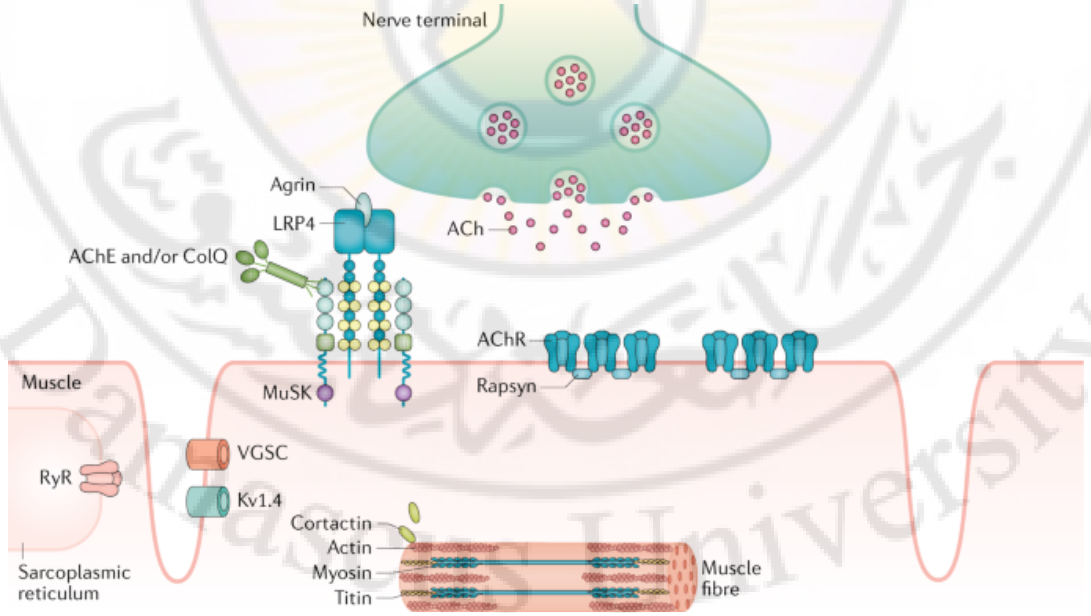


- + titin/RyR Abs in a young patient

Go and detect the presence of thymoma!!

Other Antibodies

Further Abs against extracellularly exposed antigens detected in patients with MG include anti-agrin, anti-ColQ and anti-Kv1.4. Whether they exert direct pathogenic functions remains to be determined



Other Lab tests :

RF + ANAs → rule out SLE and RA

Thyroid function tests are indicated to rule out associated Graves disease or hyperthyroidism.

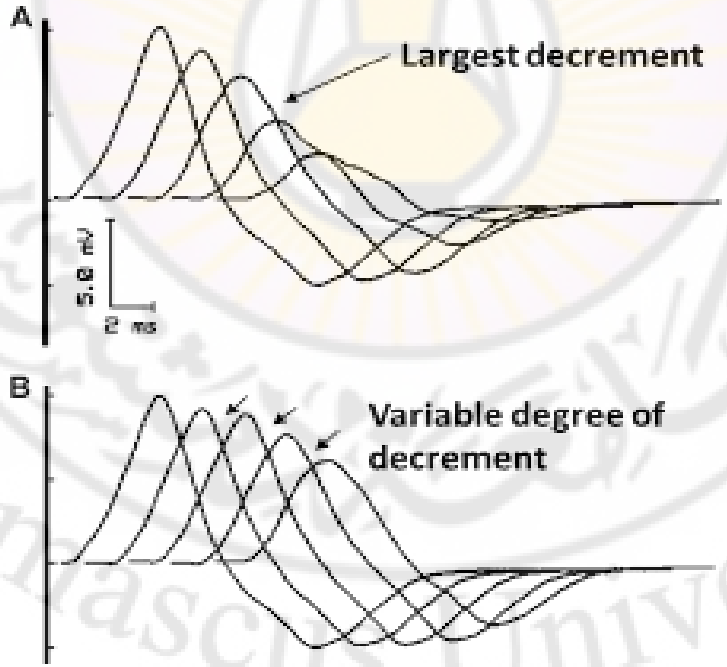
WHY ??

concomitant hyperthyroidism is frequent especially in patients with ocular MG .

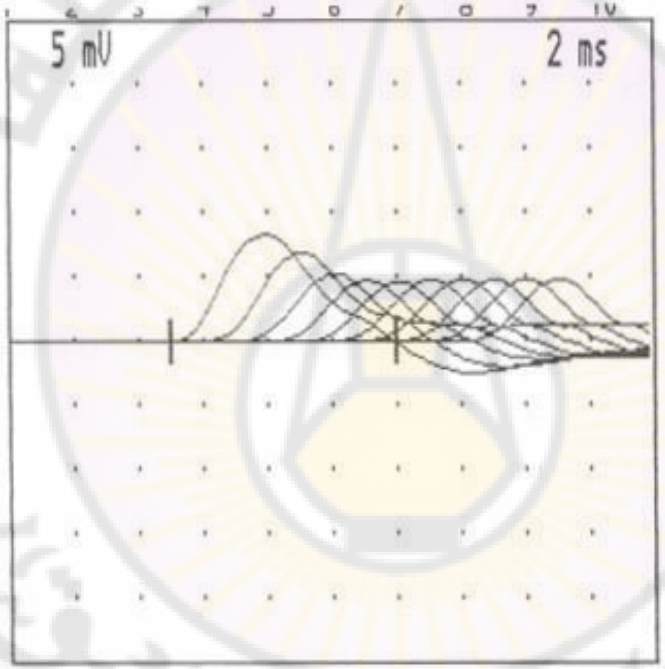
Subtype	AChR myasthenia gravis	MUSK myasthenia gravis	LRP4 myasthenia gravis	Seronegative myasthenia gravis	LEMS
					
Relative prevalence	80%	4%	2%	5%	4%

C. Electromyography

1. Repetitive Nerve Stimulation (RNS)



- **The amplitude of the fourth or fifth response** to a train of low frequency nerve stimuli **falls at least 10%** from the initial value in myasthenic patients

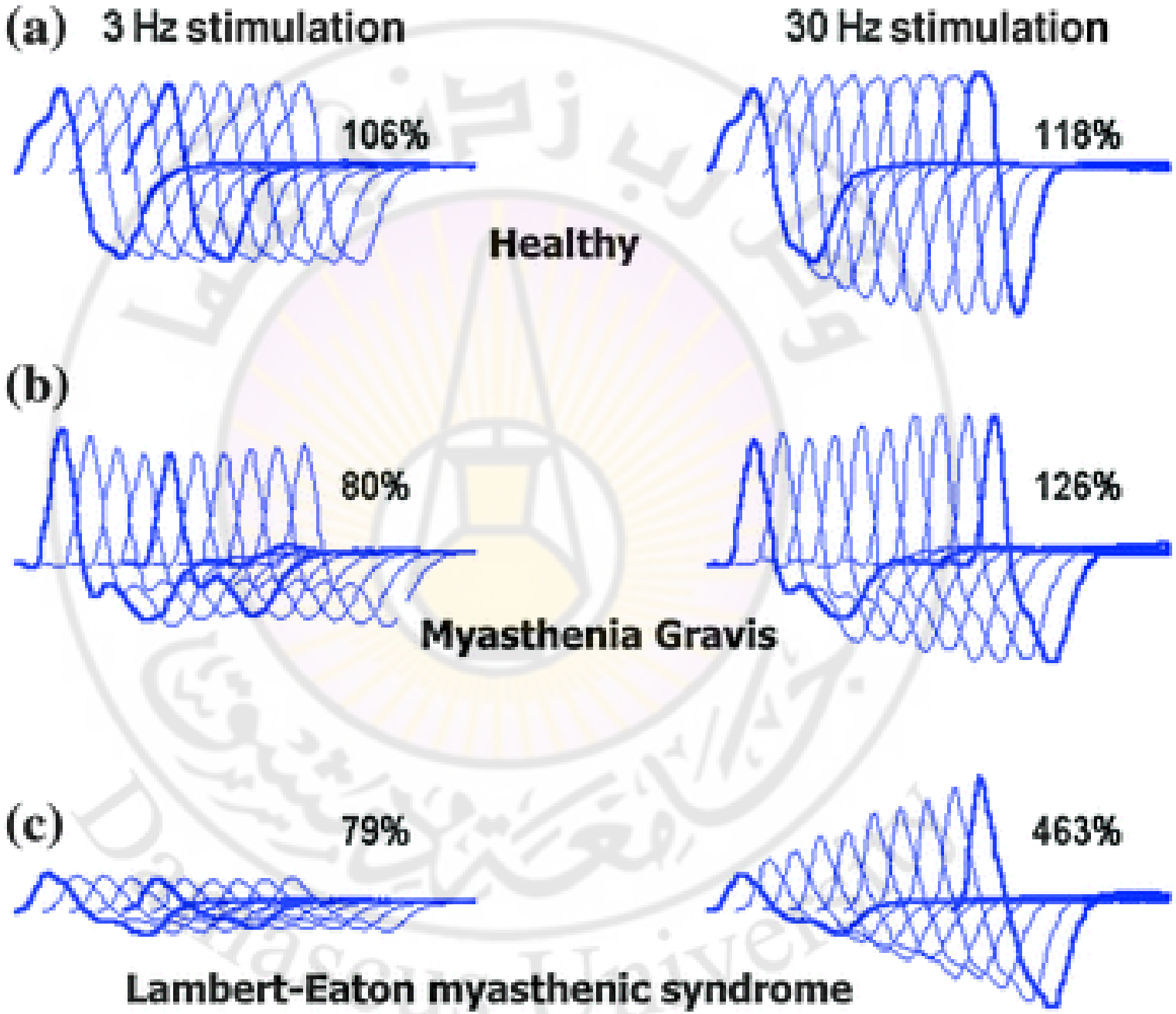


STIM.MODE: TRAIN / SINGLE

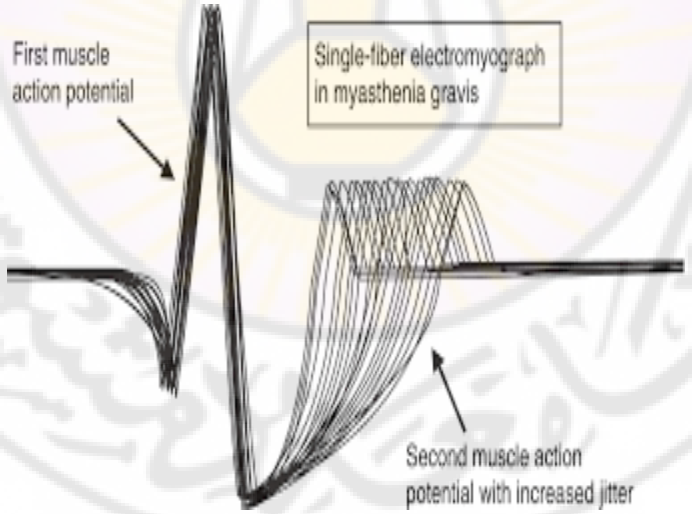
STIM FREQ: 2 Hz	NO. IN TRAIN 10
STIM DUR: 0.1 ms	STIM RJCT: 0.5 ms
TIME: 13:06:22	
COMMENT:	

POT NO.	PEAK AMP mV	AMP. DECR %	AREA mVms	AREA DECR %	STIM. LEVEL
1	8.32	0	28.20	0	175V
2	6.88	17	23.10	18	175V
3	5.32	36	17.20	39	175V
4	4.83	42	15.20	46	175V
5	4.76	43	14.60	48	175V
6	4.86	42	15.30	46	175V
7	4.83	42	15.70	44	175V
8	4.84	42	15.30	46	175V
9	4.84	42	15.60	45	175V
10	4.90	41	15.40	45	175V

Seen more in proximal muscles (e.g the facial muscles and deltoid) than the hands.


(a) 3 Hz stimulation
30 Hz stimulation
106%
118%
Healthy
(b)
80%
126%
Myasthenia Gravis
(c)
79%
463%
Lambert-Eaton myasthenic syndrome

2. Single Fiber EMG (SFEMG)



CAUTION :

In STRICTLY OCULAR MG

It is essential to rule out mass lesions compressing the cranial nerves through performing a CT/MRI of the brain and orbit

MRI can evaluate for intraorbital or intracranial lesions, basal meningeal pathology, or multiple sclerosis

Subtypes of MG are broadly classified as follows:

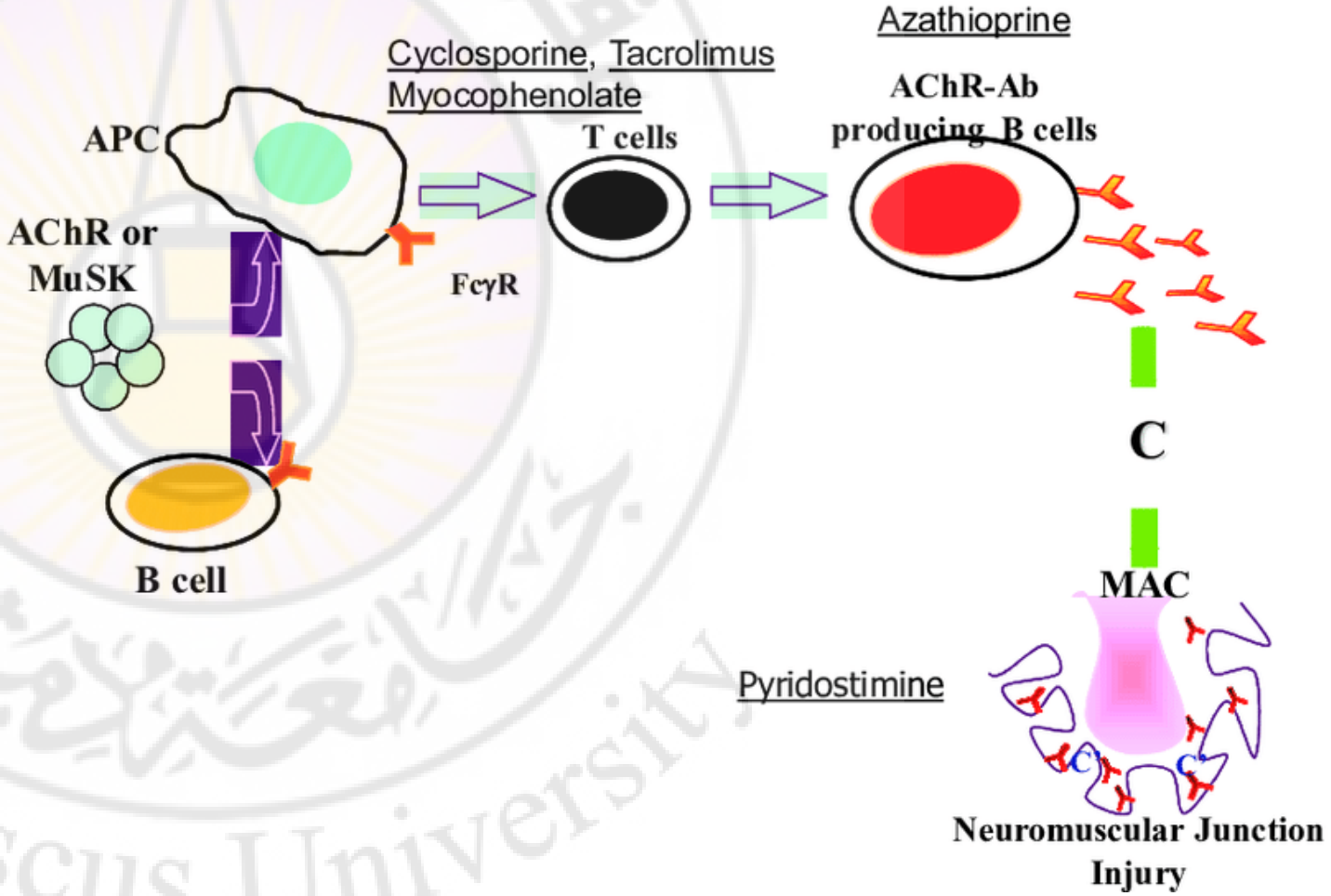
1. Early-onset MG: age at onset <50 years. Thymic hyperplasia, usual females.
2. Late-onset MG: age at onset >50 years. Thymic atrophy, mainly males.
3. Thymoma-associated MG (10%–15%)
4. MG with anti-MUSK antibodies.
5. Ocular MG (oMG): symptoms only affecting extraocular muscles.
6. MG with no detectable AChR and muscle-specific tyrosine kinase (MuSK) antibodies.

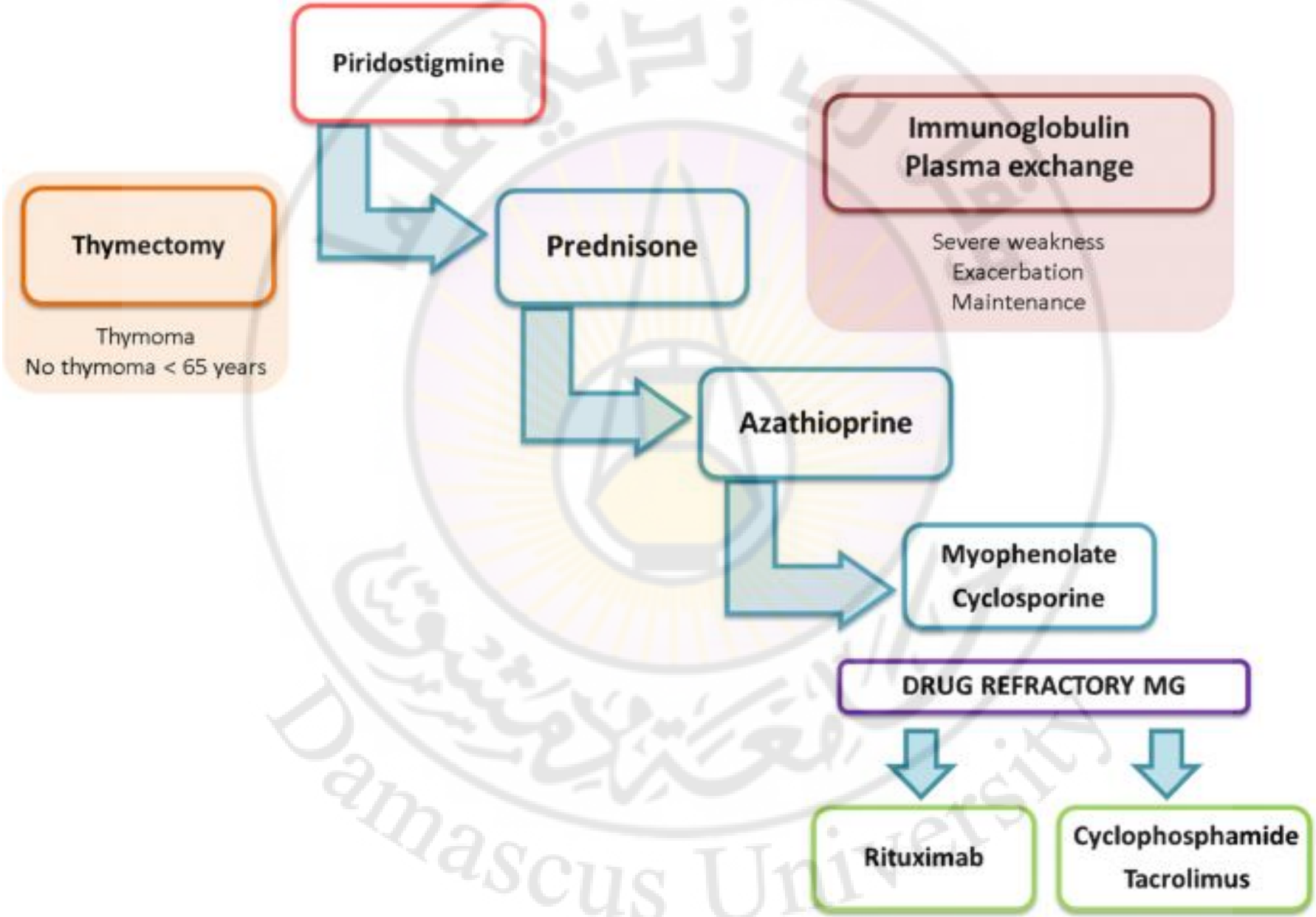
MEDICAL MANAGEMENT:

- **Cholinesterase inhibitors**
- **Corticosteroids**
- **Immunosuppressant**

Plasmapheresis

IVIG




Piridostigmine
Immunoglobulin
Plasma exchange
Severe weakness
Exacerbation
Maintenance
Thymectomy
Thymoma
No thymoma < 65 years
Prednisone
Azathioprine
Myophenolate
Cyclosporine
DRUG REFRACTORY MG
Rituximab
Cyclophosphamide
Tacrolimus

CHE Inhibitors

Mestinon (Pyridostigmine bromide) first choice, dose 30-60 mg q 6-8 h/daily

Prostigmine (Neostigmine bromide) 7.5 – 15.0 mg q 6-8 h/daily

No fixed dosage schedule suits all patients

CHE Inhibitors

The need for ChE inhibitors varies from day to day and during the same day

Different muscles respond differently with any dose, certain muscles get stronger, others do not change and still others become weaker

The drug schedule should be titrated according to the pateints work load and muscle activity

Prednisone

Marked improvement or complete relief of symptoms occurs in 75% of cases

Improvement in first 6 to 8 weeks, but strength may increase to total remission over months

Best responses in patients with recent onset MG, but chronic disease may also respond

Prednisone

The severity of the disease does not predict the ultimate improvement

Patients with thymoma have an excellent response to prednisone before or after thymectomy

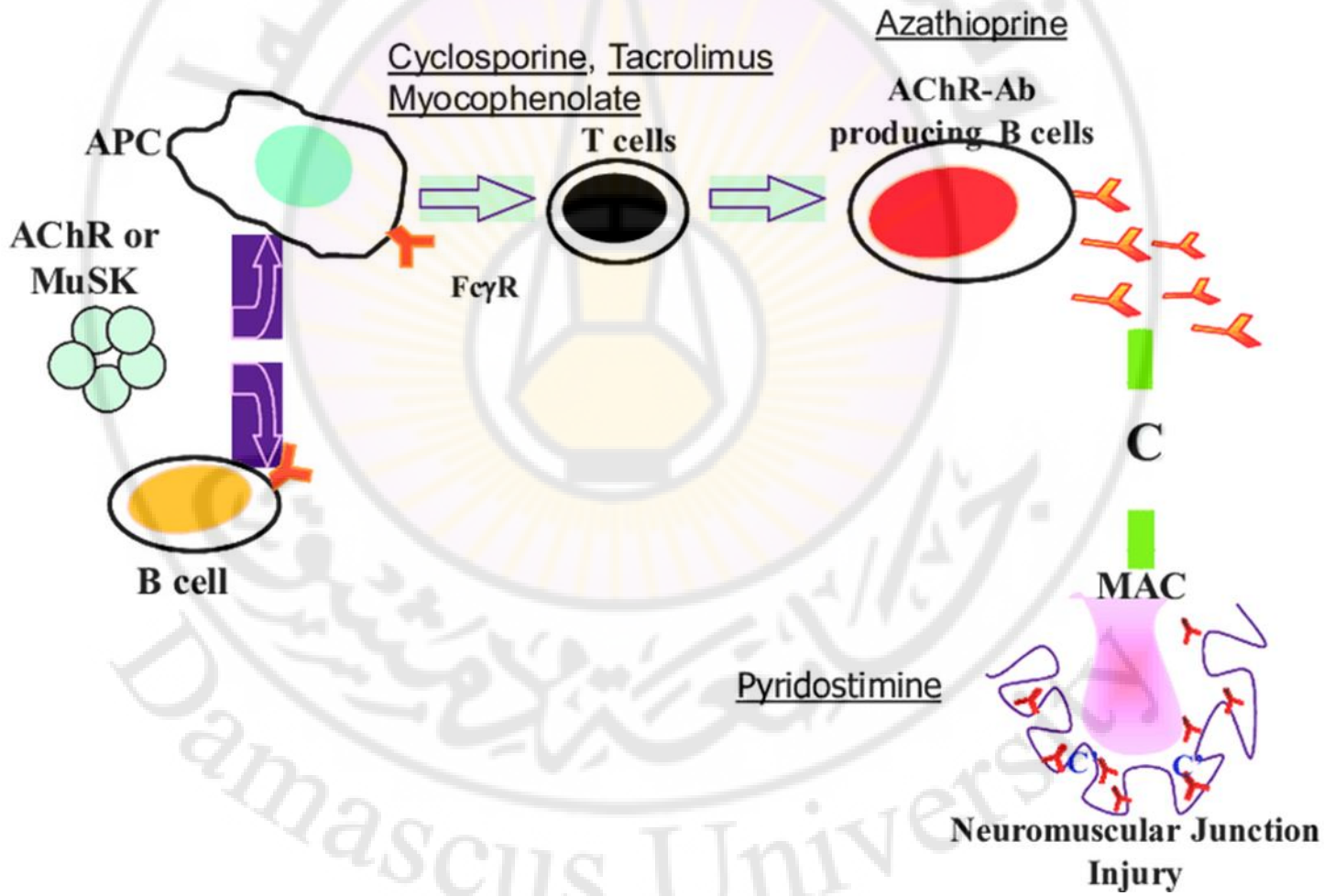
Prednisone

Prednisone 60 to 80 mg/day given until sustained improvement (usually 2 weeks) then alternate days beginning with 100-120 mg tapered over months to lowest dose necessary (usually less than 20 mg alternate days)

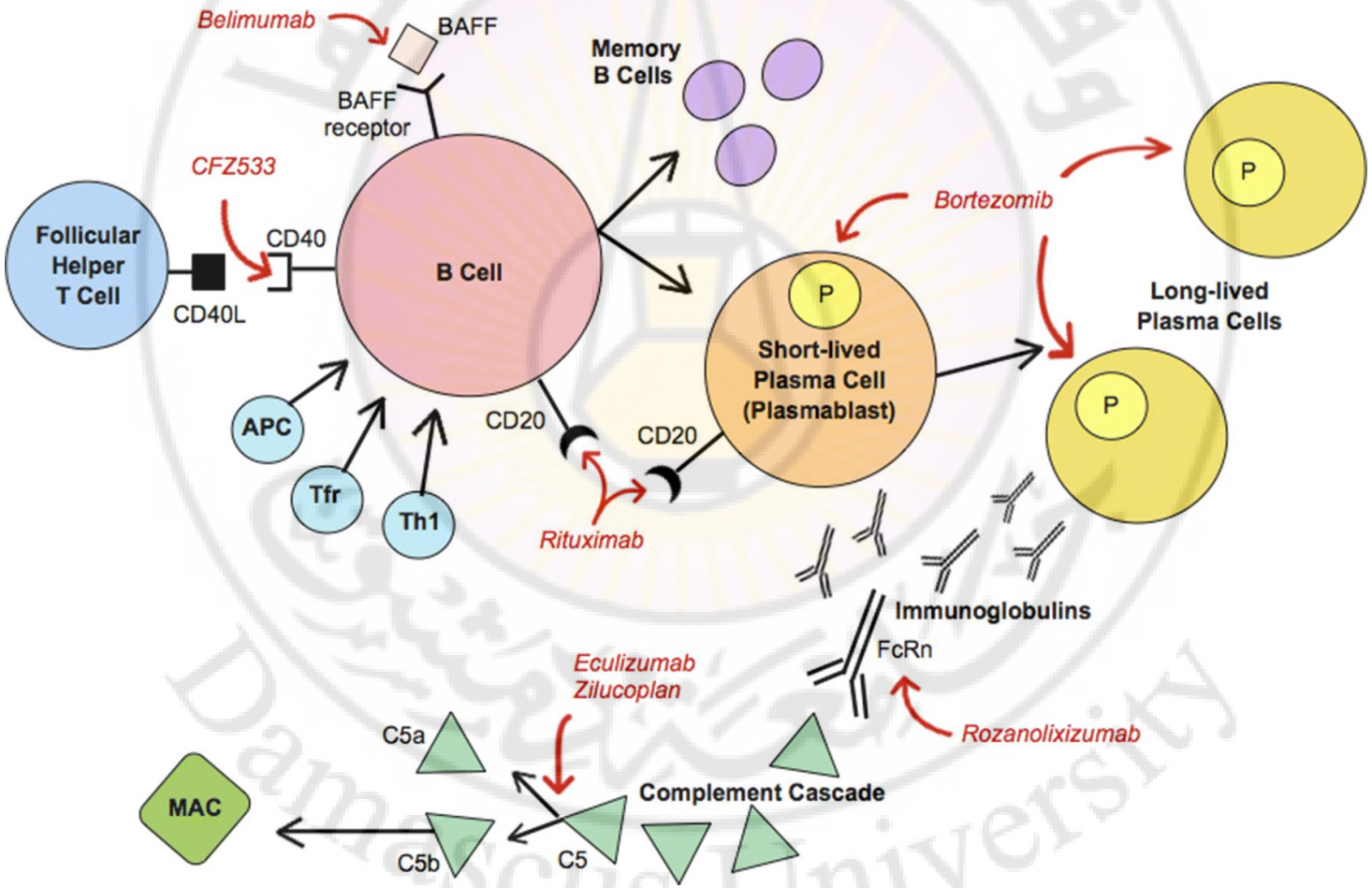
Immunomodulators

- Azathioprine, mycophenolate mofetil, cyclosporine, cyclophosphamide, and rituximab

Immunomodulators



Immunomodulators



Rituximab

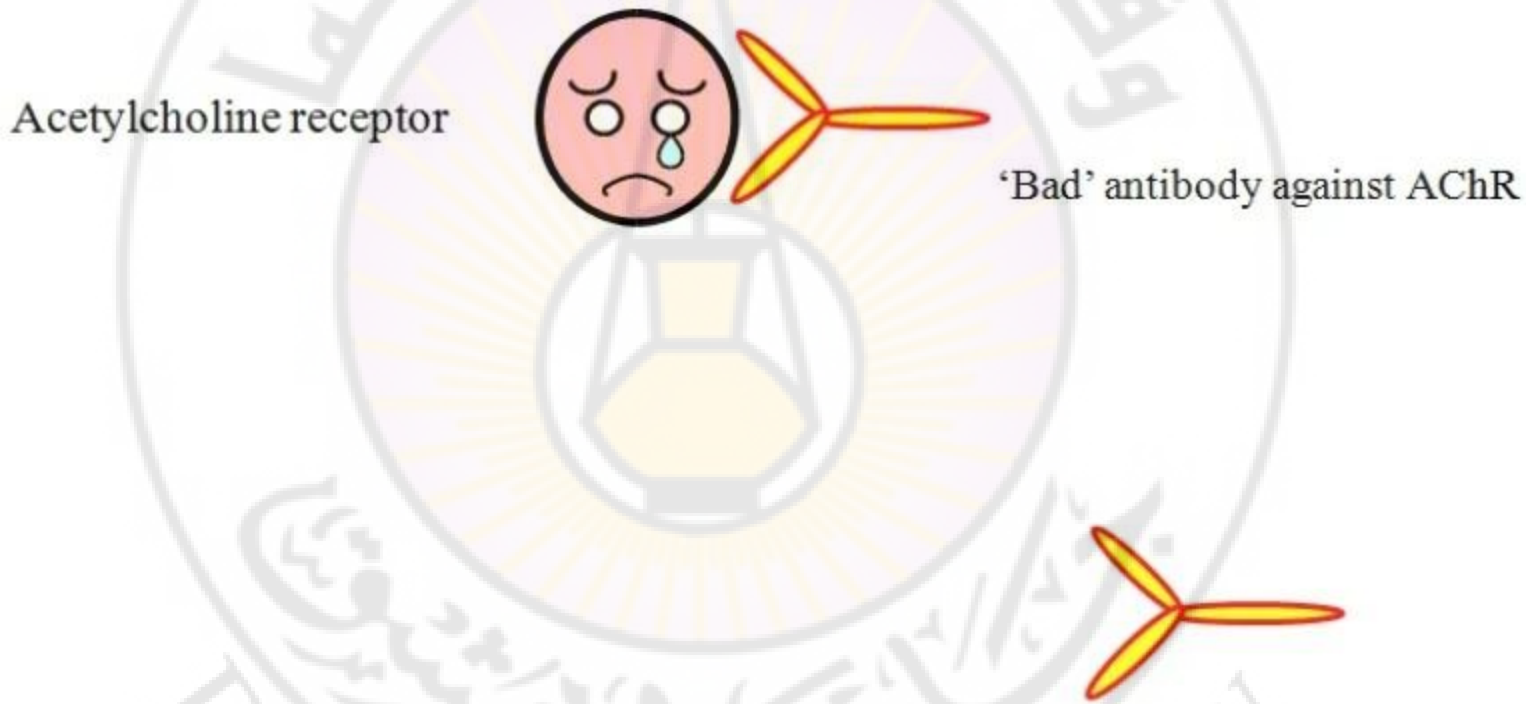
- Rituximab has emerged as a potentially effective therapeutic option for treatment of MG when first- and second-line immunotherapy fails. Patients with anti-MuSK-Ab-associated MG respond well to rituximab. On the other hand, they tend not to respond well to first-line immunotherapy.

IVIG

- IVIg is effective in moderate or severe MG worsening into crisis, but it does not exhibit value in mild disease.
- Studies reveal that patients who have moderate or severe MG (ie, who are not in crisis) do not show an improvement in function or a reduced need for steroids.
- Data neither support or rule out a role for IVIg in chronic MG. To be included in IVIg studies, patients have been required to be autoantibody-positive. Therefore, the use of IVIg in a seronegative patient is not supported by the literature

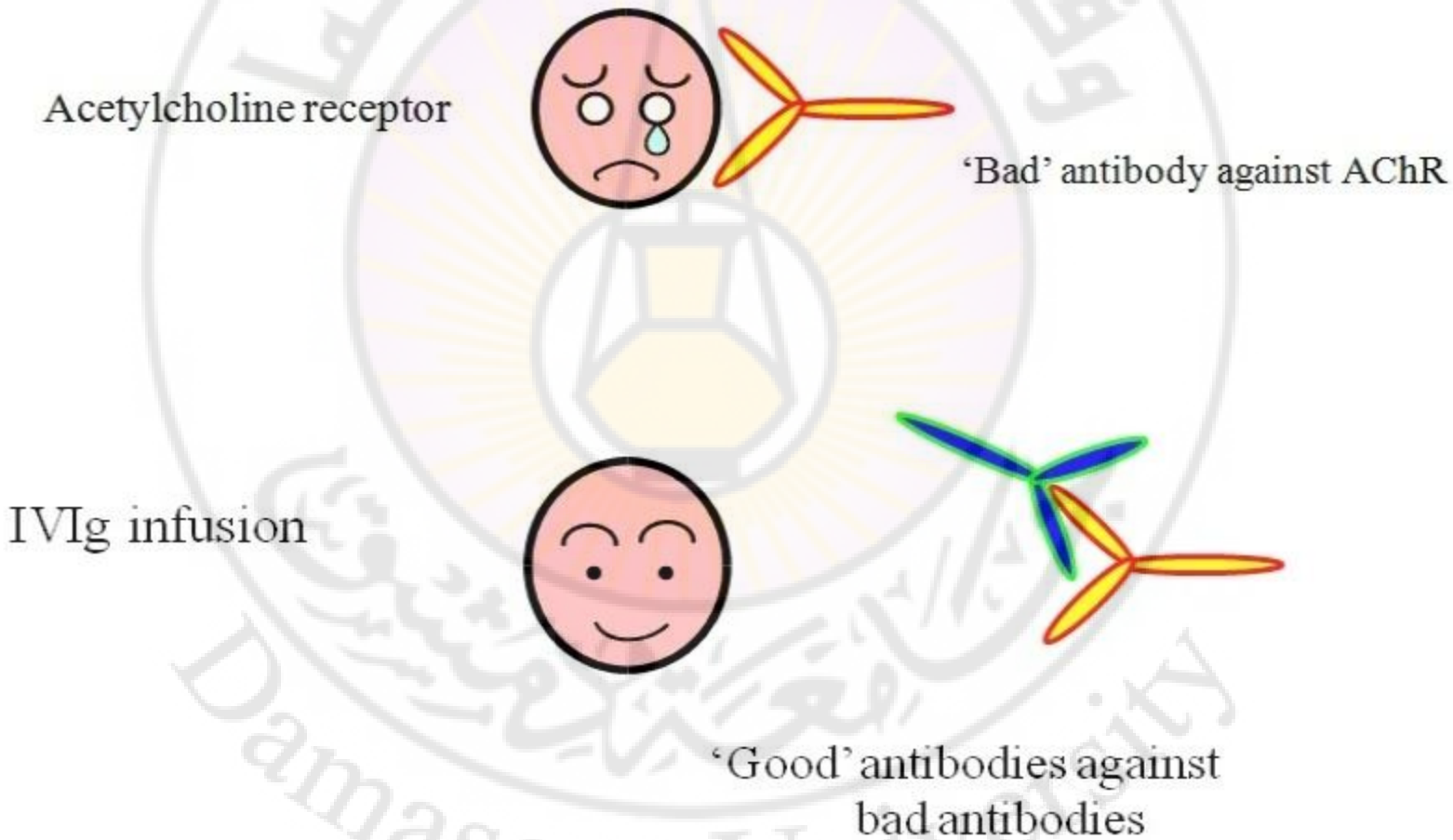
How does IVIg work in MG?

One possible mechanism

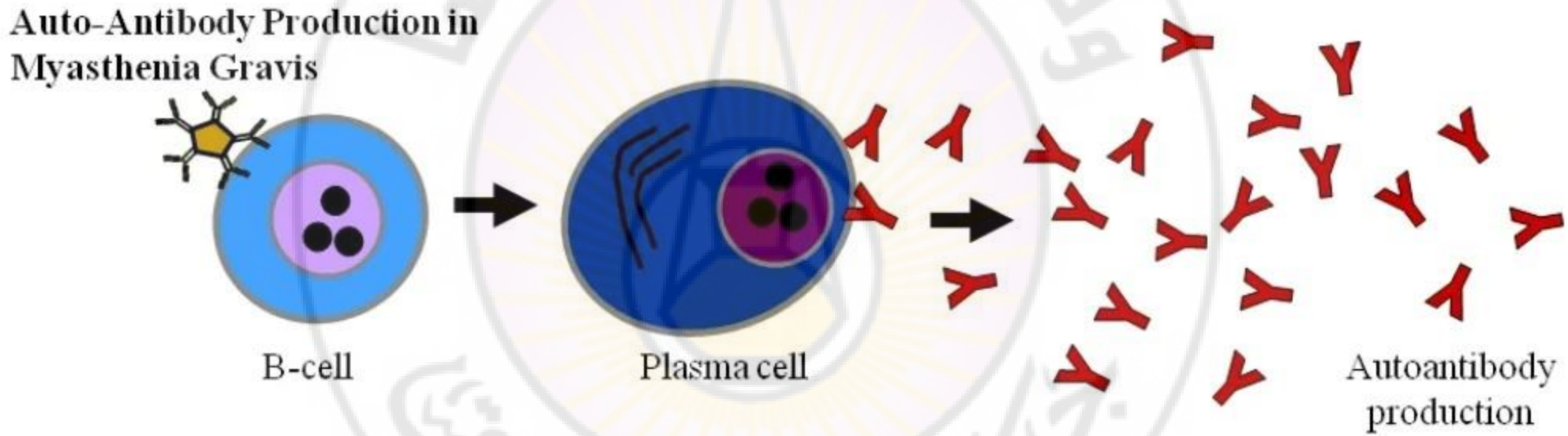


How does IVIg work in MG?

One possible mechanism



The presence of large amounts of IgG will also suppress the production of host IgG



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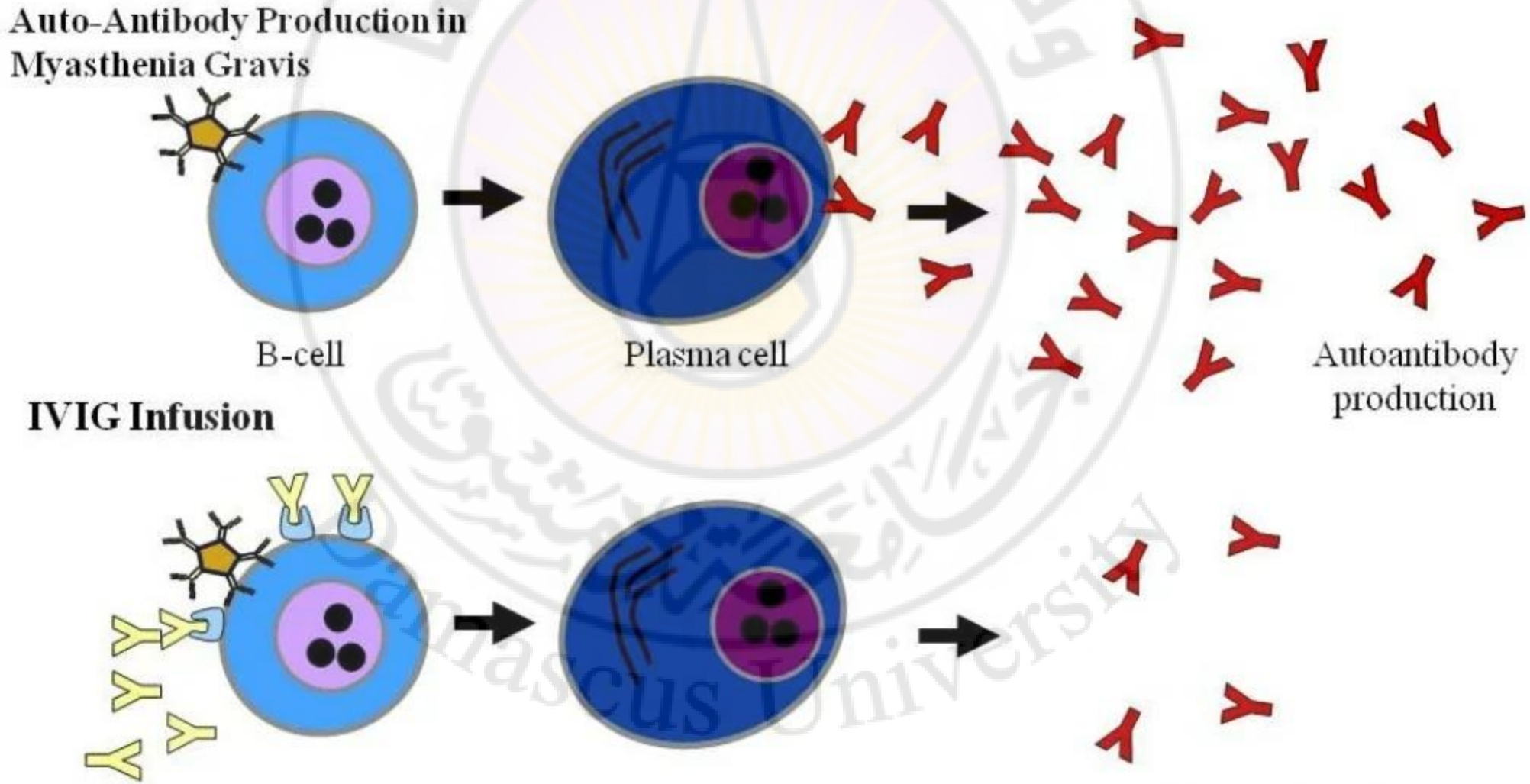


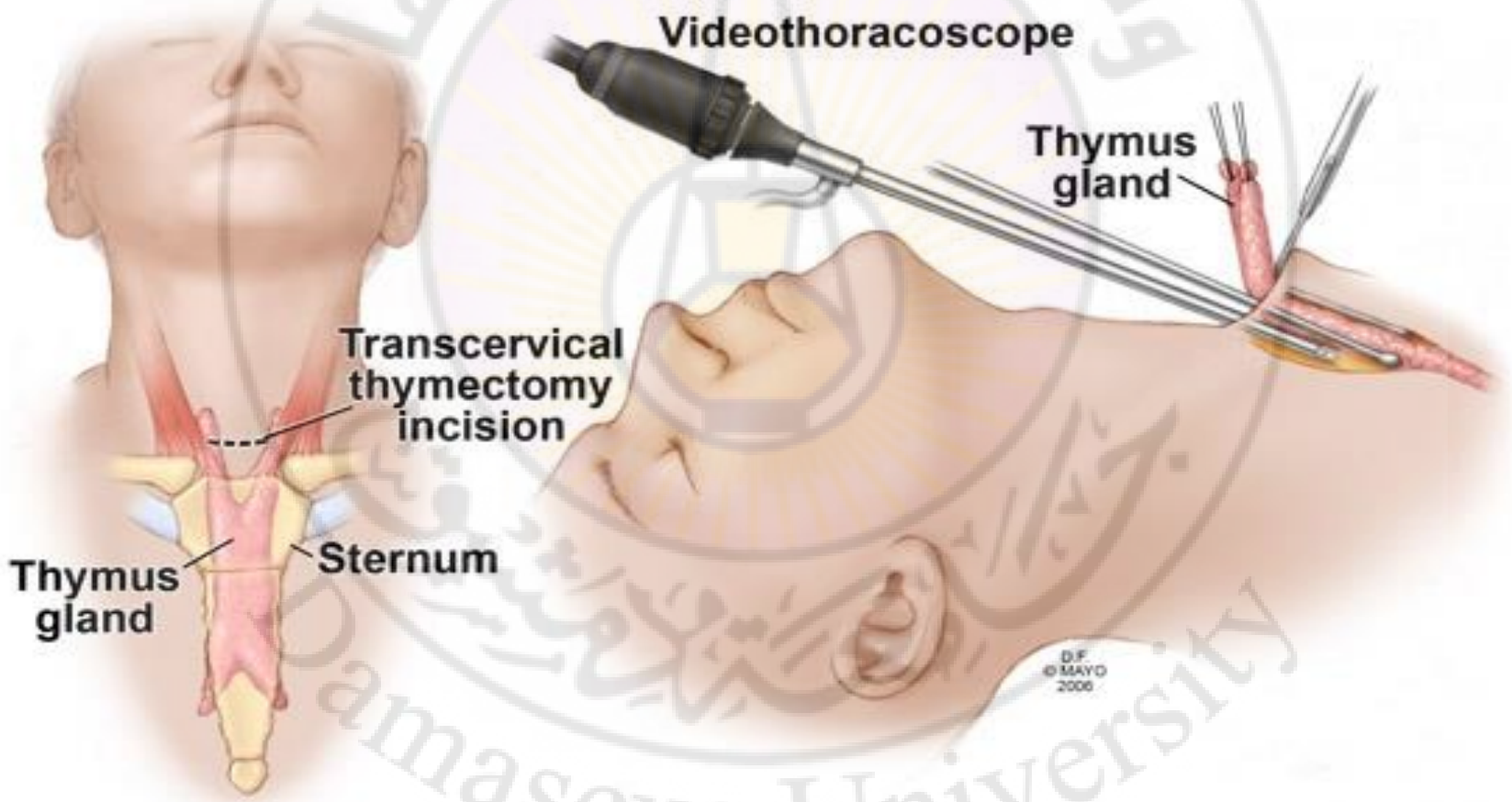
Plasmapheresis

- Plasmapheresis (plasma exchange) is believed to act by removing circulating humoral factors (ie, anti-AChR antibodies and immune complexes) from the circulation. It is used as an adjunct to other immunomodulatory therapies and as a tool for crisis management. Like IVIg, plasmapheresis is generally reserved for myasthenic crisis and refractory cases. Improvement is noted in a couple of days, but it does not last for more than 2 months

Plasmapheresis

- Plasmapheresis is an effective therapy for MG, especially in preparation for surgery or as short-term management of an exacerbation. Improvement in strength may help to achieve rapid postoperative recovery and to shorten the period of assisted ventilation. Long-term regular plasmapheresis on a weekly or monthly basis can be used if other treatments cannot control the disease.

SURGICAL MANAGEMENT



- Even though no controlled trial to assess the efficacy of thymectomy in MG has been reported, this procedure has become the standard of care and is indicated for all patients with thymoma and for patients aged 10-55 years without thymoma but with generalized MG. Thymectomy has been proposed as a first-line therapy in most patients with generalized myasthenia. Research is under way to determine whether thymectomy combined with prednisone therapy is more beneficial in treating nonthymomatous MG than prednisone therapy alone.

- Thymectomy is not recommended in patients with antibodies to muscle-specific kinase (MuSK), because of the typical thymus pathology, which is very different from the more common type of MG characterized by seropositivity for AChR antibodies. [49]

MYASTHENIC CRISIS

- **A rapid and severe deterioration of myasthenia** called "myasthenic crisis" can bring patient to the brink of respiratory failure and quadriparesis in hours
- A respiratory infection or a sedative medication with NM block may be the reason
- It can develop at any time after the diagnosis of myasthenia
- Anticipate if patient is restless, anxious with diaphoresis and develops tremor.
- **Require respiratory support**

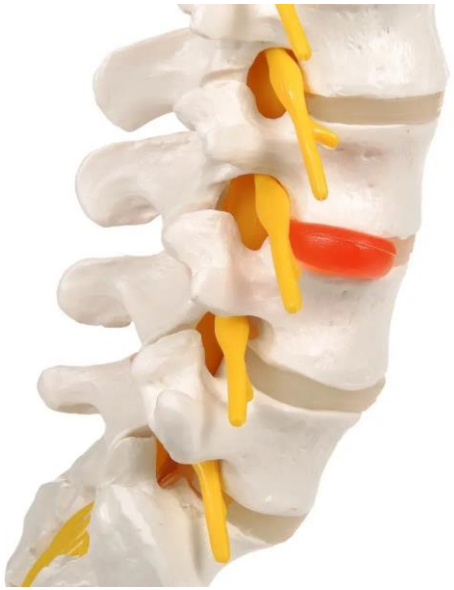
Difference between Myasthenic Crisis and Cholinergic Crisis

Myasthenic Crisis	Cholinergic Crisis
Under medication	Overmedication
Temporary improvement of symptoms with administration of Edrophonium	Symptoms improve with administration of anticholinergics (Atropine)
Heart rate increased	Heart rate decrease
Respiratory distress	Abdominal cramps
Pupil : Mydriasis	Pupil: Miosis
Increased Blood pressure	Decreased blood pressure
Normal secretion	Increased secretion

THANK YOU

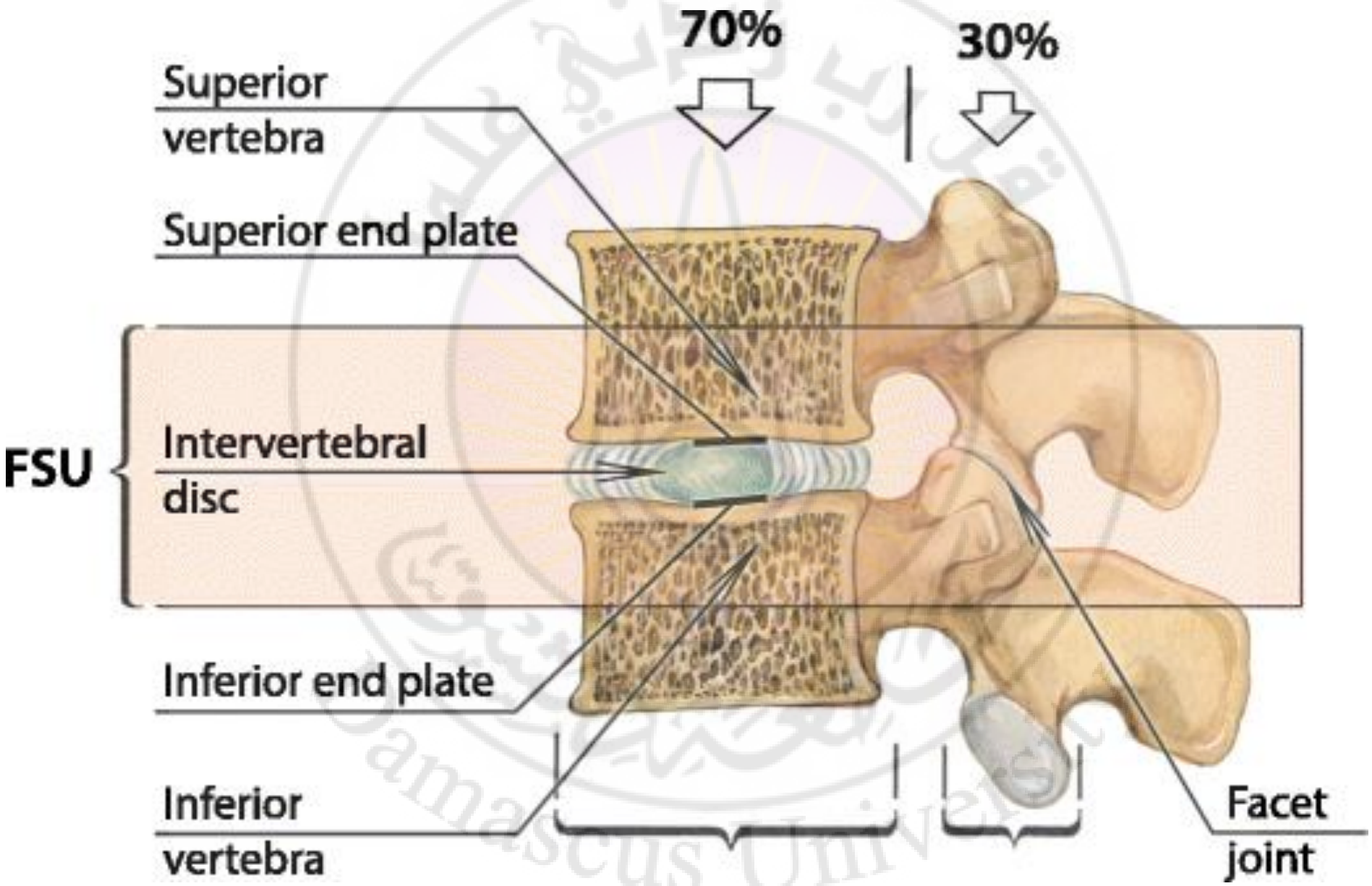
بسم الله الرحمن الرحيم

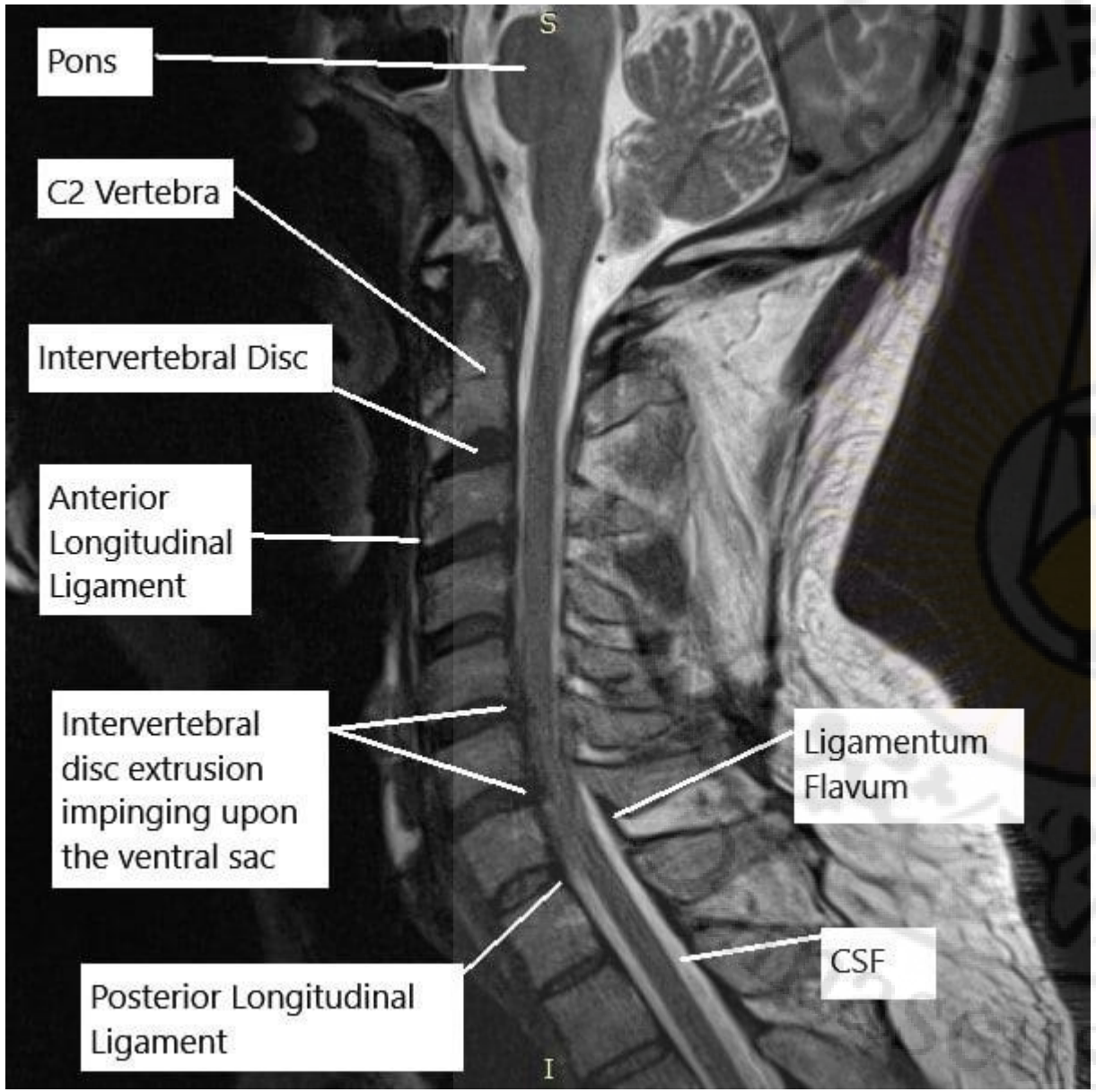
Nerve Root, Nerve Plexus and Peripheral Nerve Lesions

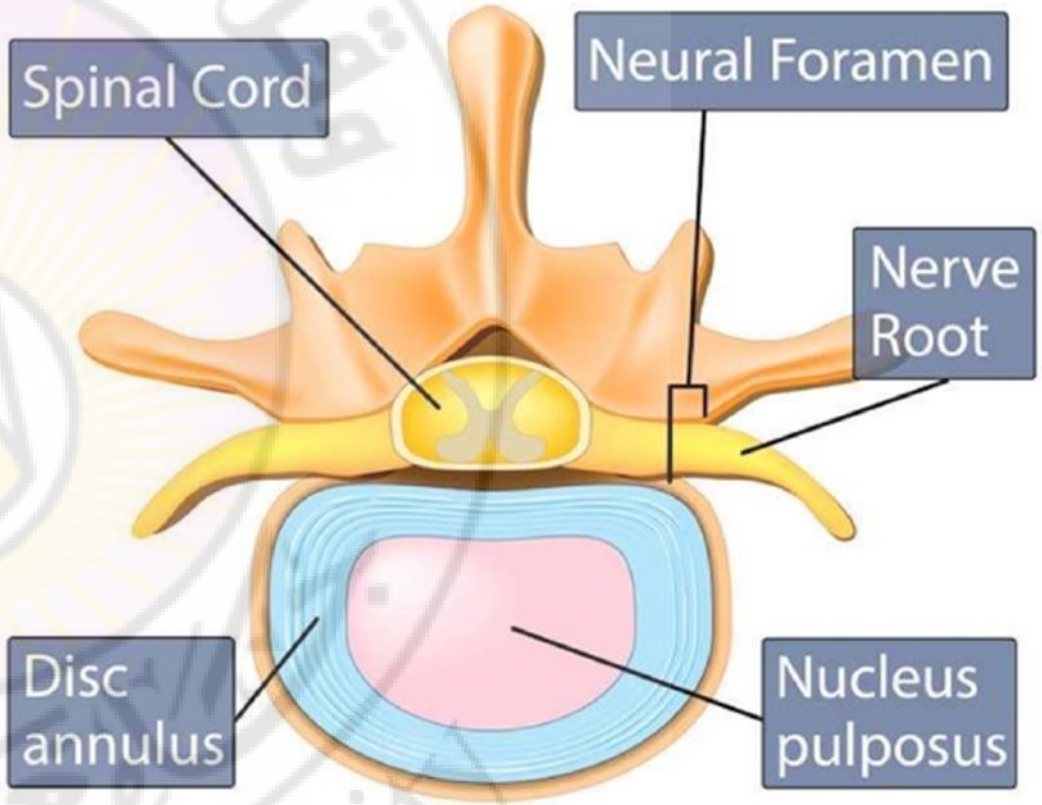


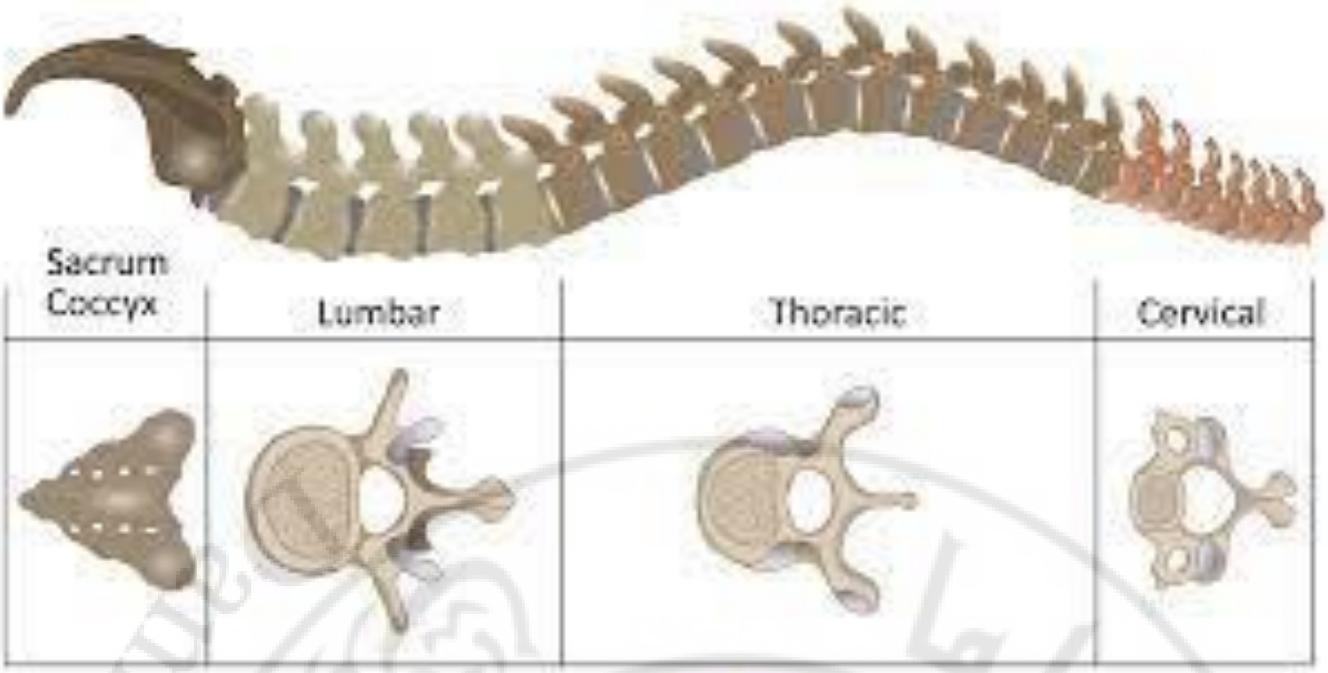
Prof. Mohamad Shehadeh Agha

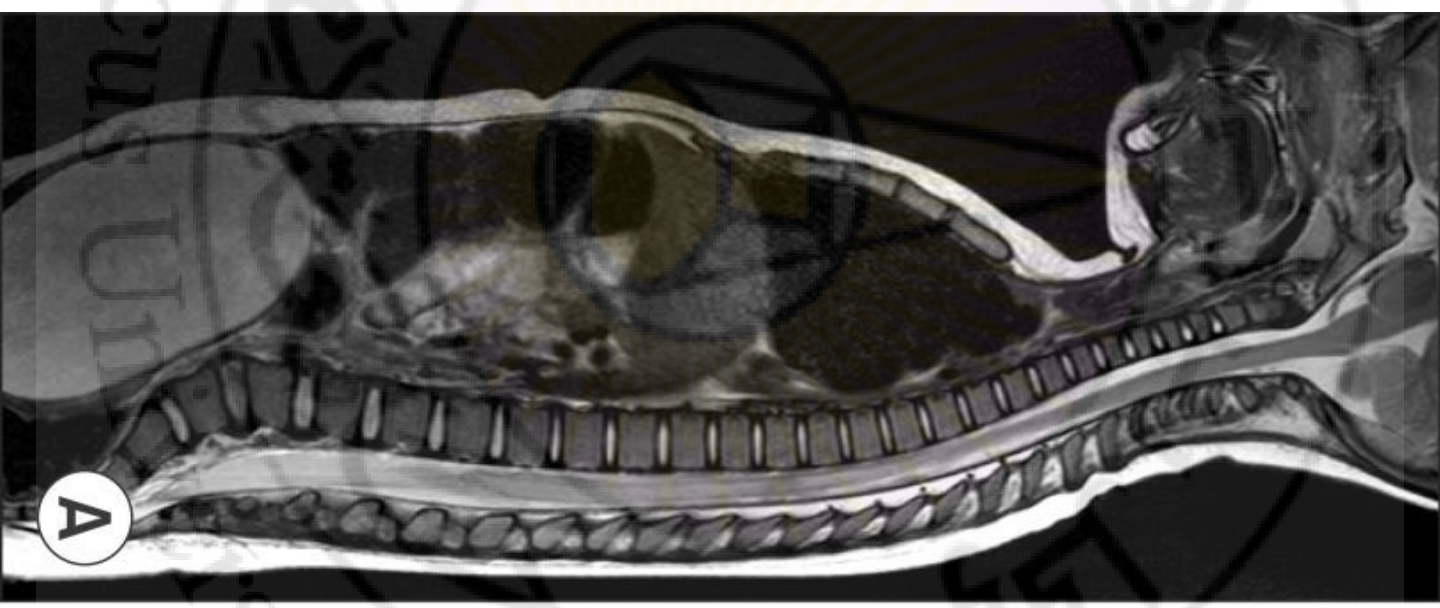
MD MRCP (London) FRCP (Edin)


70%
30%
Superior vertebra
Superior end plate
FSU
Intervertebral disc
Inferior end plate
Inferior vertebra
Facet joint


Pons
C2 Vertebra
Intervertebral Disc
Anterior Longitudinal Ligament
Intervertebral disc extrusion impinging upon the ventral sac
Posterior Longitudinal Ligament
Ligamentum Flavum
CSF
S
I


Spinal Cord
Neural Foramen
Nerve Root
Disc annulus
Nucleus pulposus


Sacrum
Coccyx
Lumbar
Thoracic
Cervical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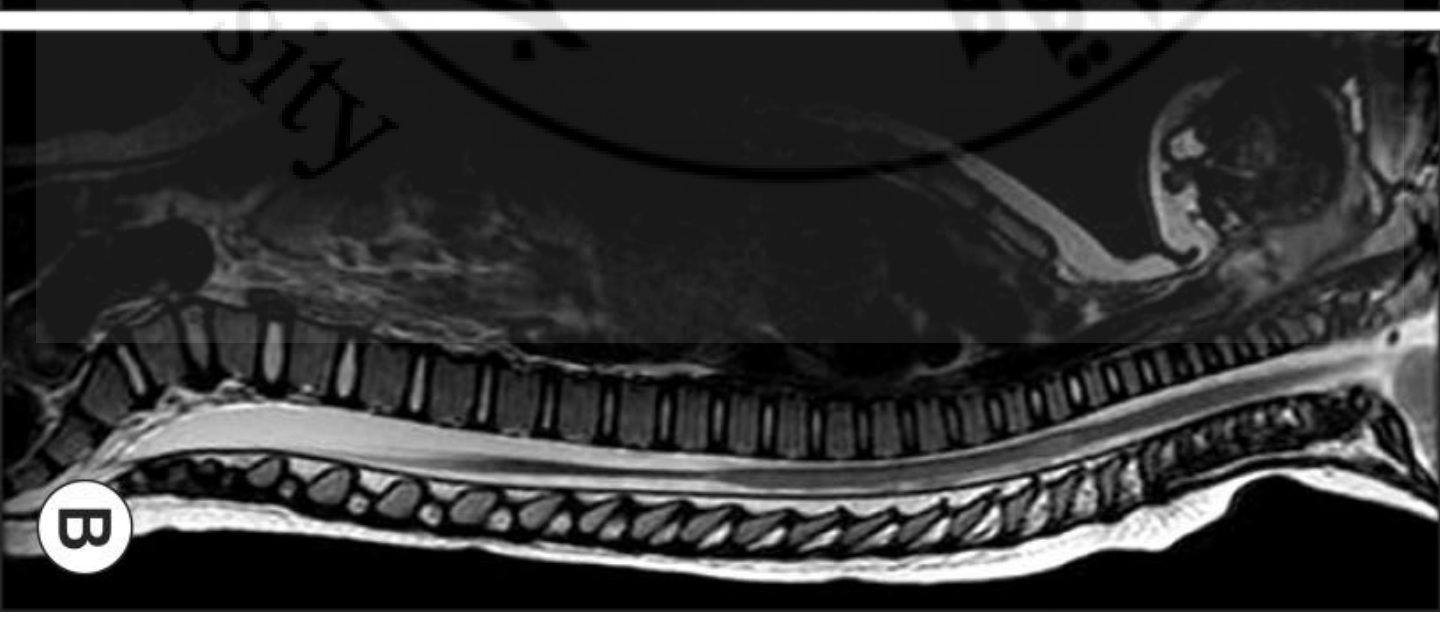
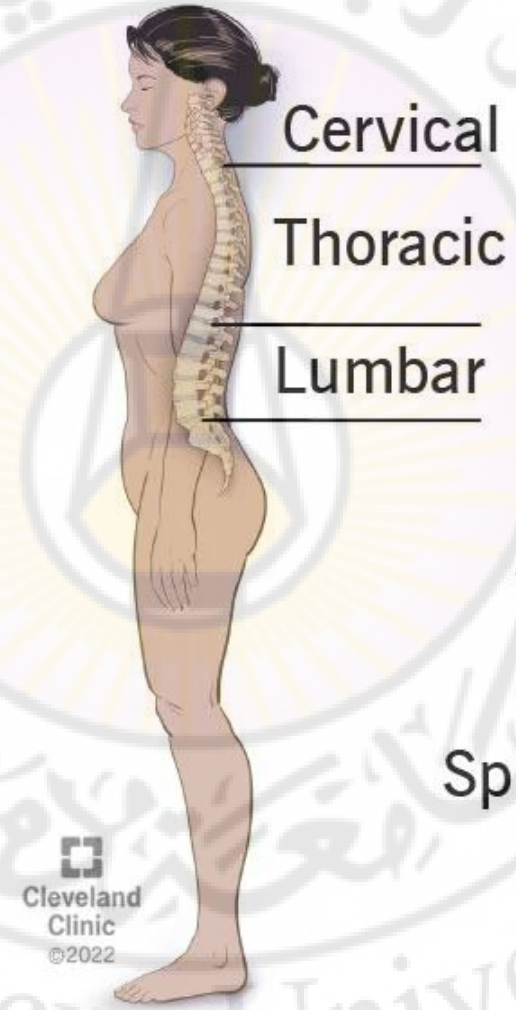
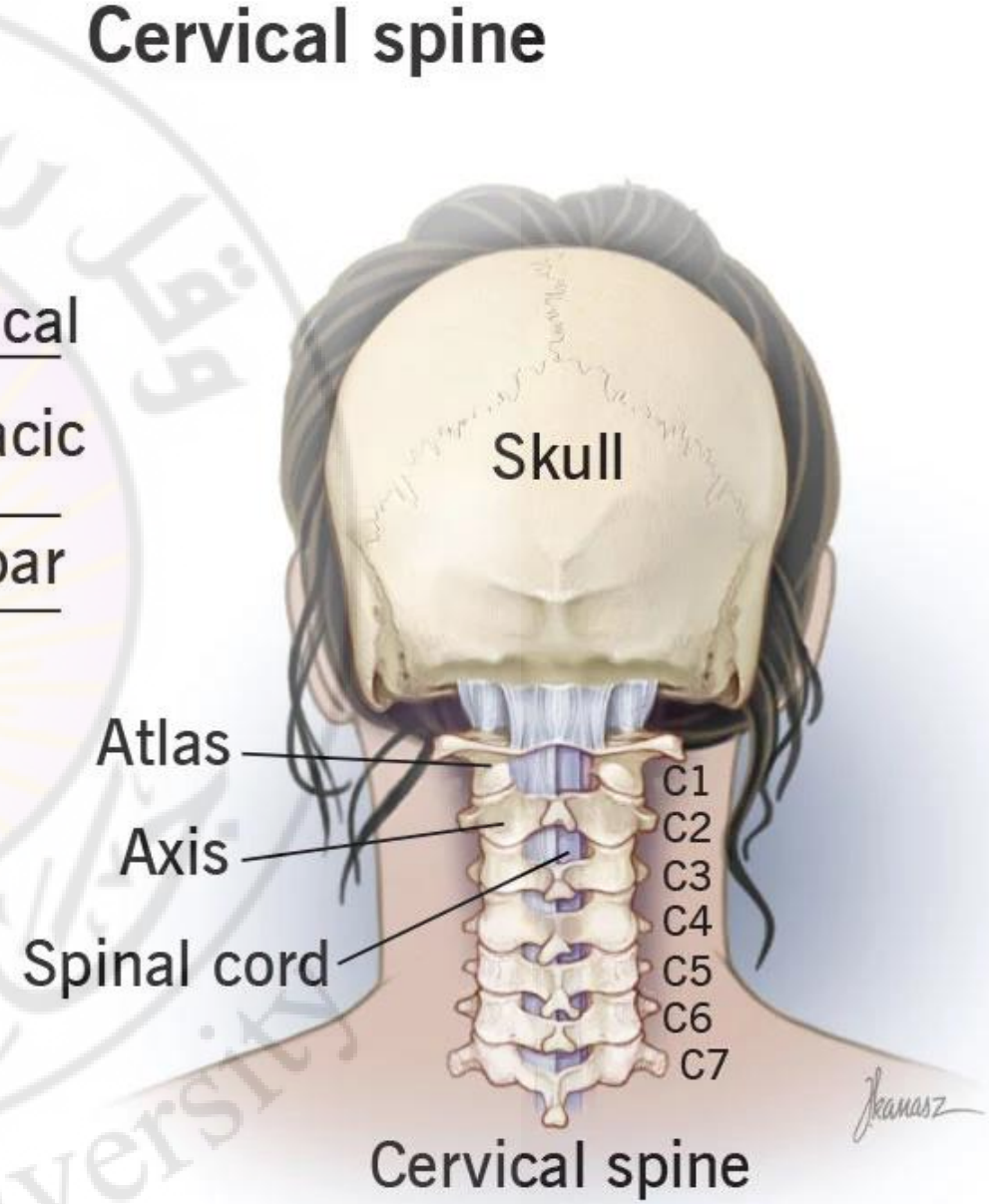
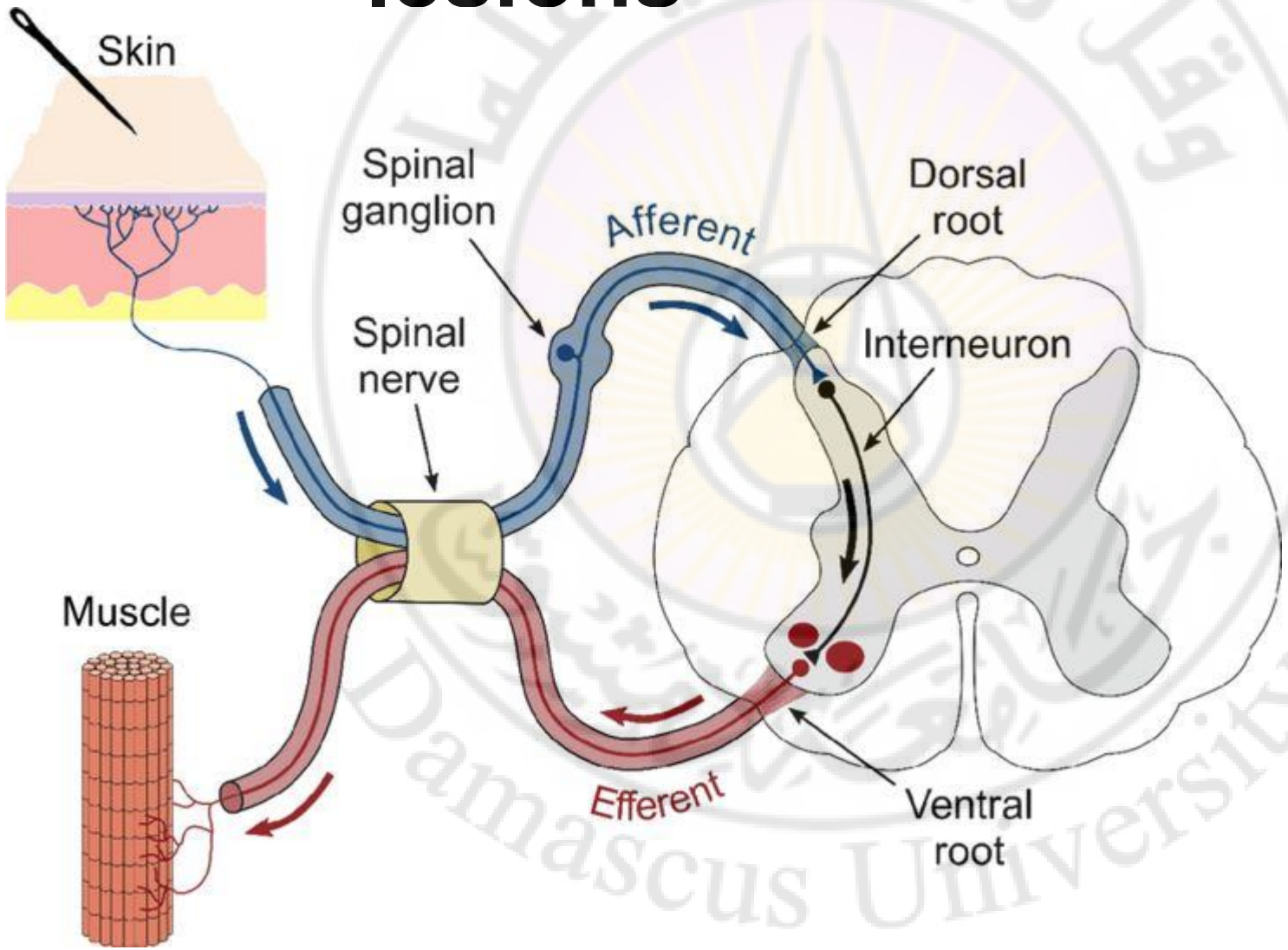

B


Cervical Spine
Atlas (C1)
Axis (C2)
C3
C4
C5
C6
C7
VERITAS health


Cervical
Thoracic
Lumbar
Cleveland Clinic
©2022

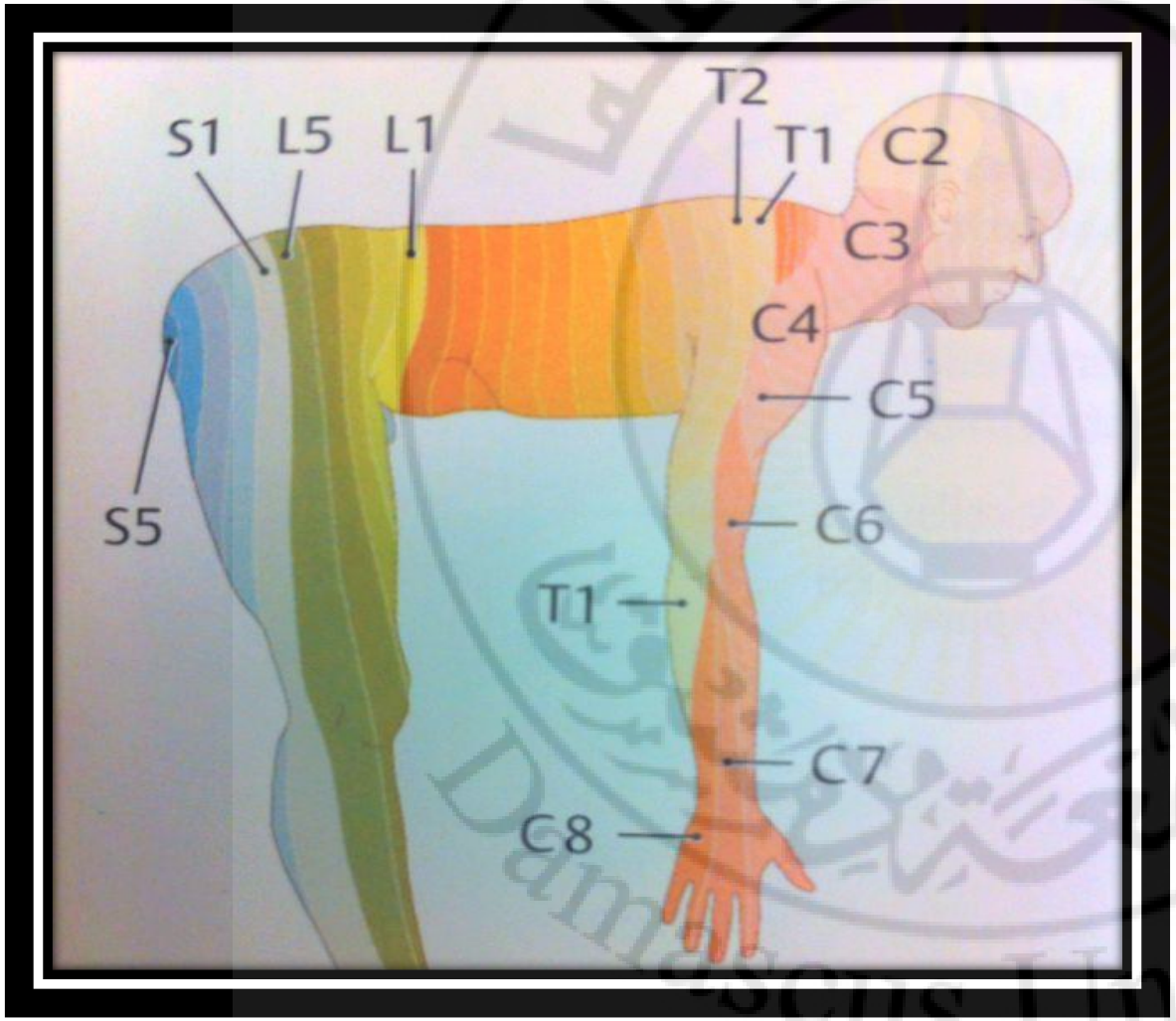

Cervical spine
Skull
Atlas
Axis
Spinal cord
C1
C2
C3
C4
C5
C6
C7
Jkanasz
Cervical spine

Nerve root lesions

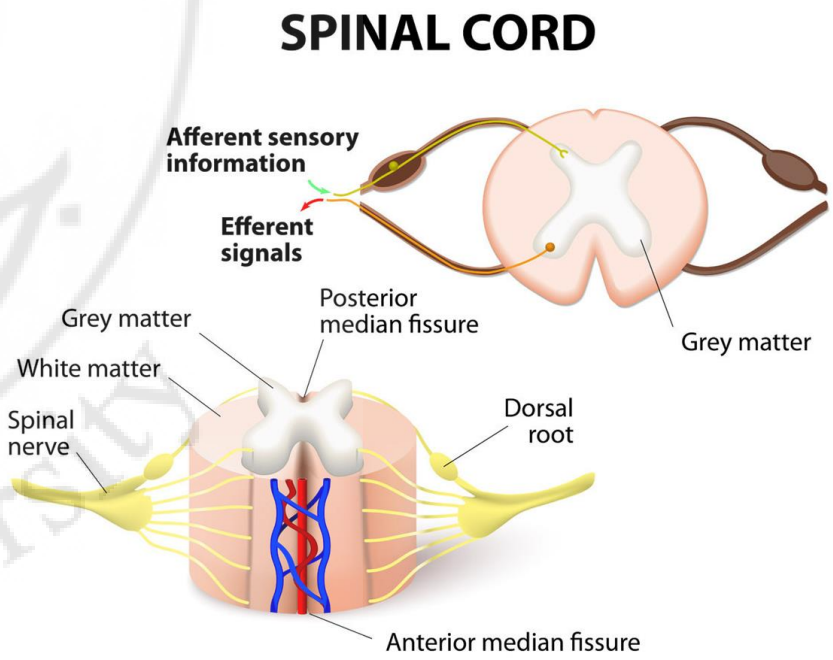


A nerve root lesion, or radiculopathy, suggests a lesion involving the dorsal and ventral nerve roots and/or the spinal nerve.

Nerve root lesions



A nerve root lesion, or radiculopathy, suggests a lesion involving the dorsal and ventral nerve roots and/or the spinal nerve.

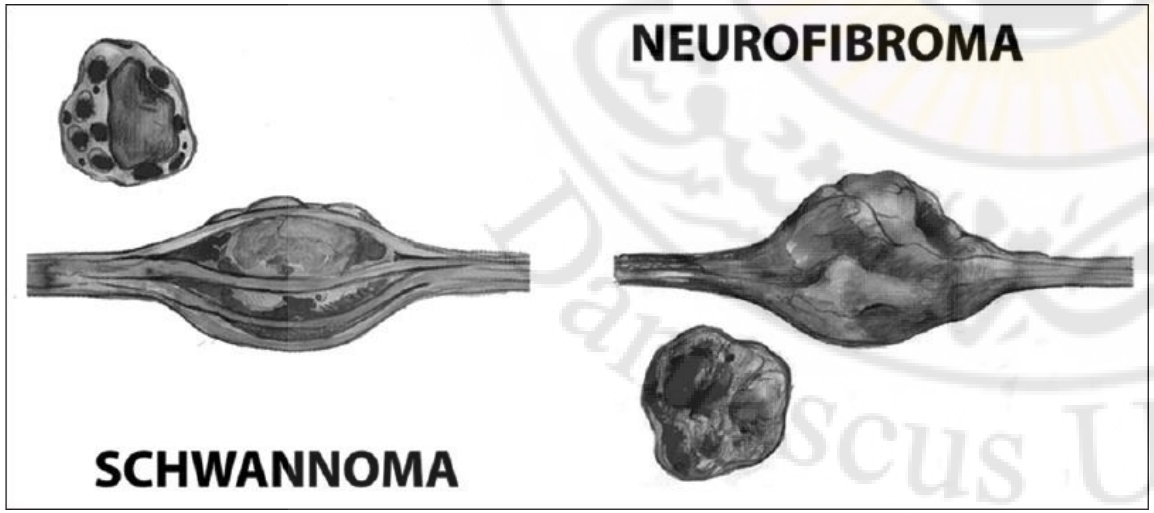


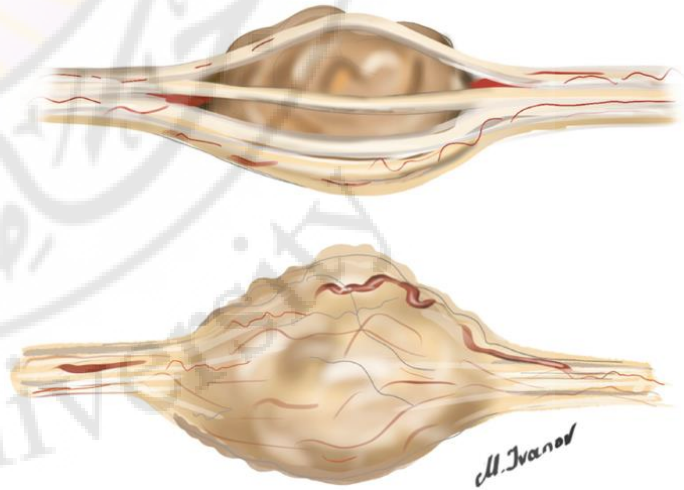
Nerve root lesions

The common syndromes associated with pathology of the nerve roots and spinal nerves are:

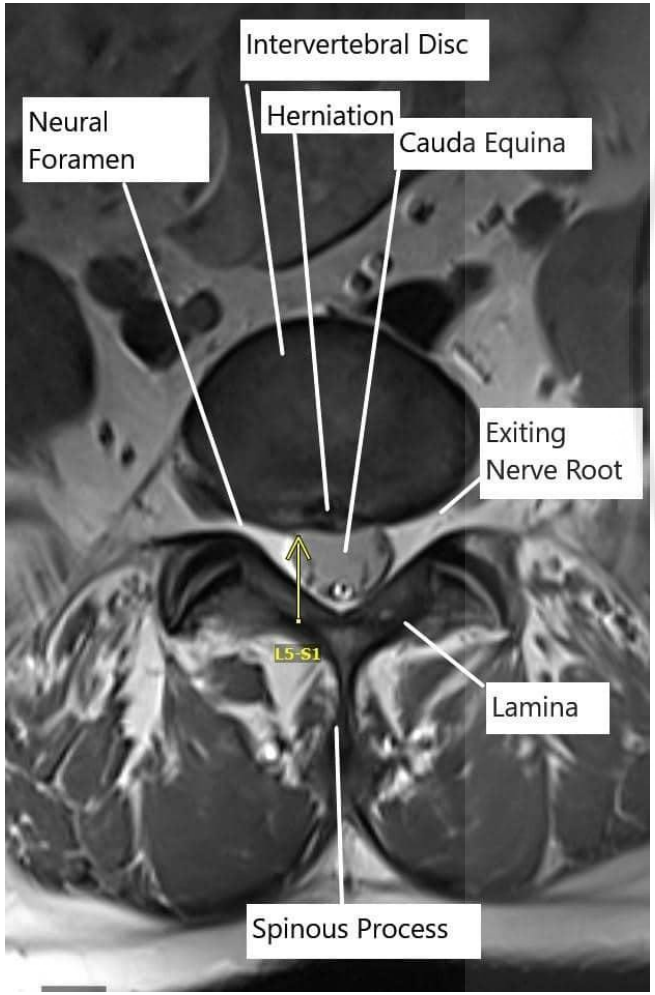
- prolapsed intervertebral disc
- herpes zoster
- metastatic disease in the spine

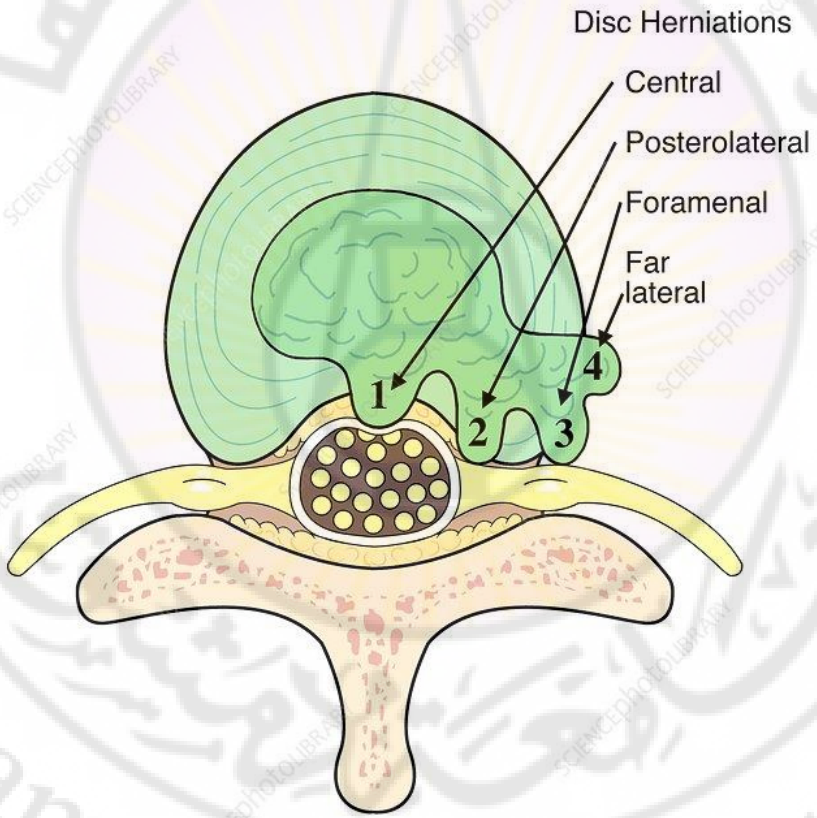
Less common is the compression of these structures by a neurofibroma and schwannoma

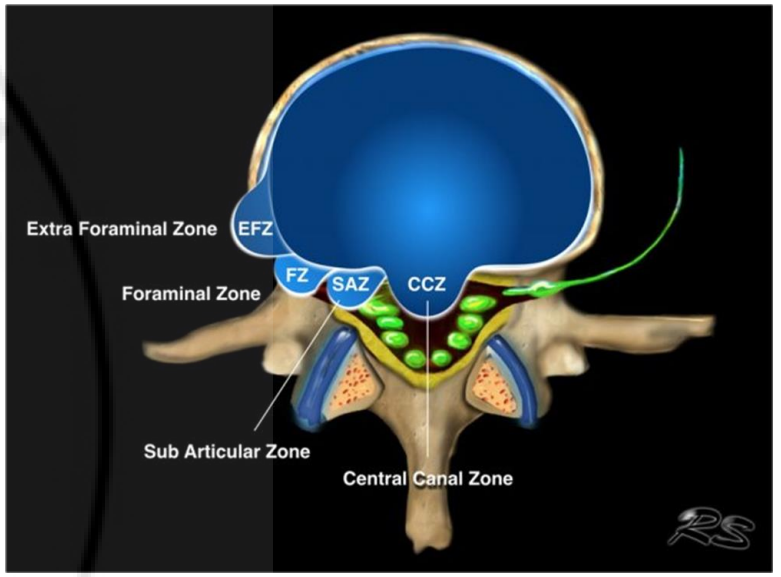


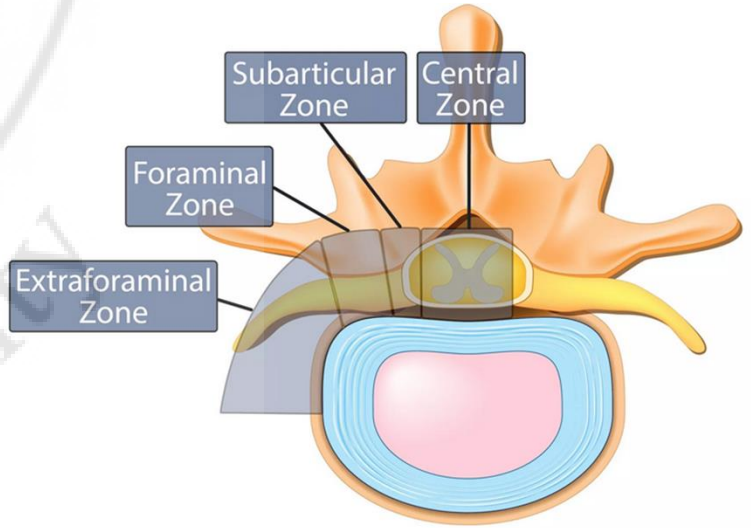


Nerve root lesions



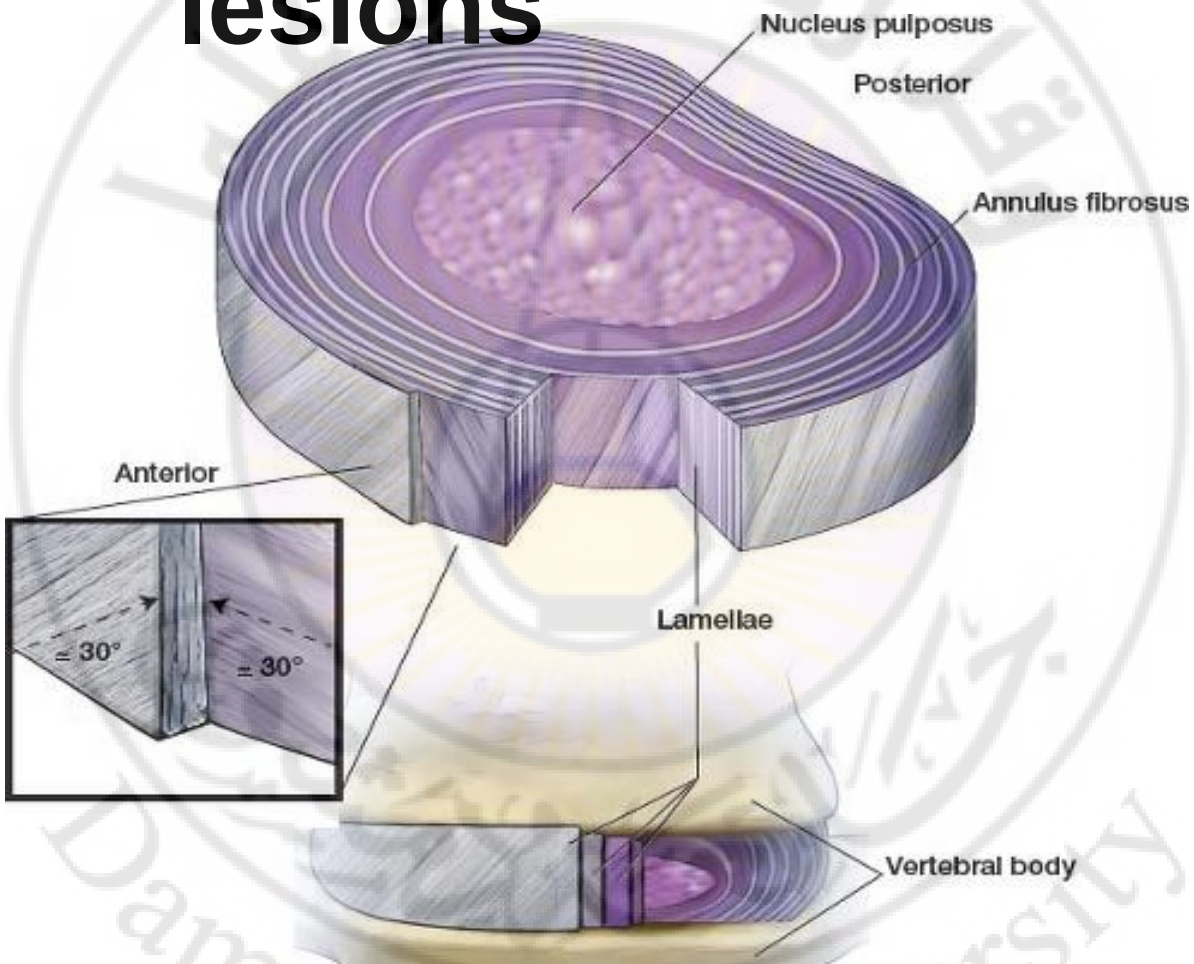




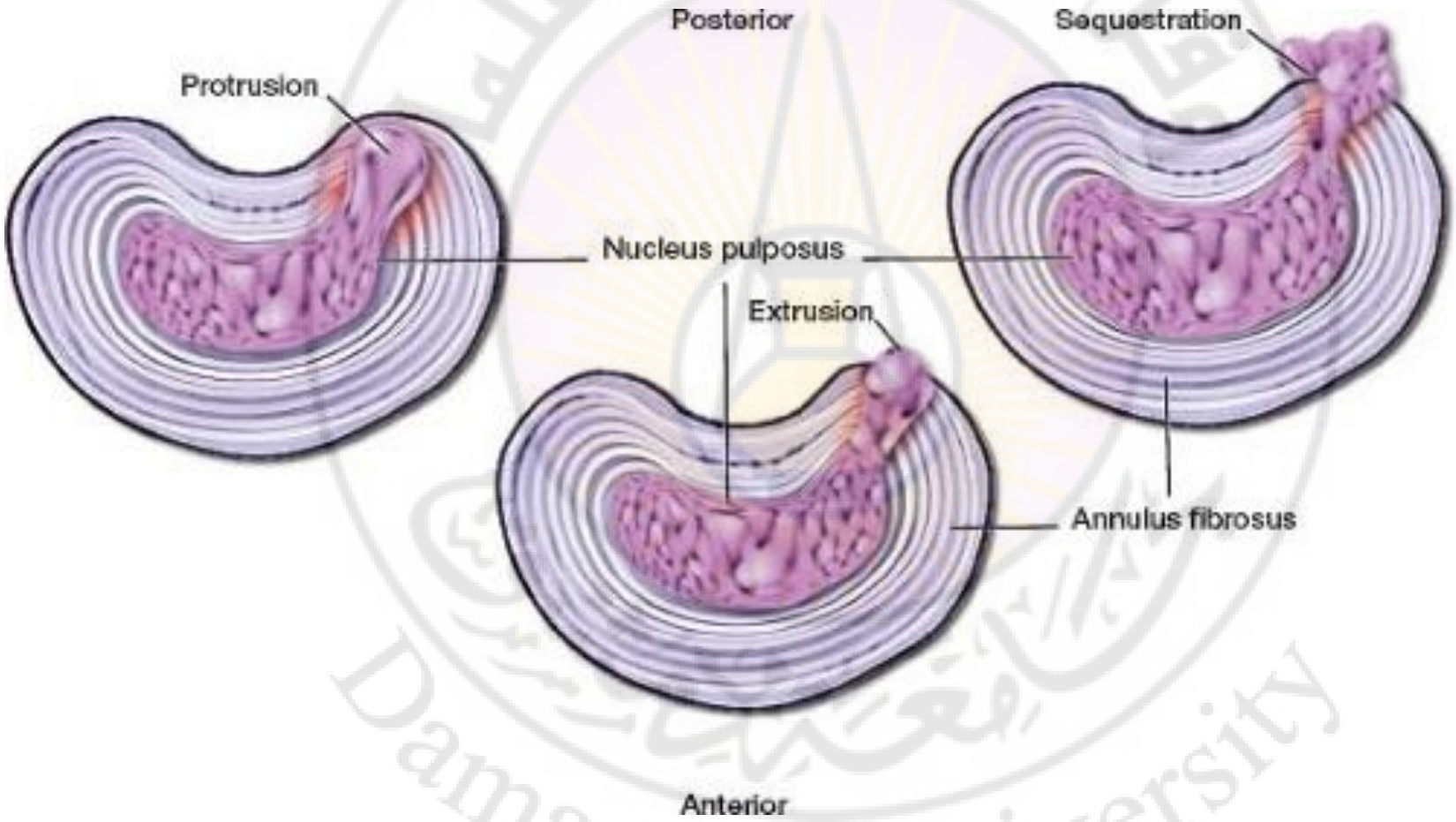


Prolapsed intervertebral disc

Nerve root lesions

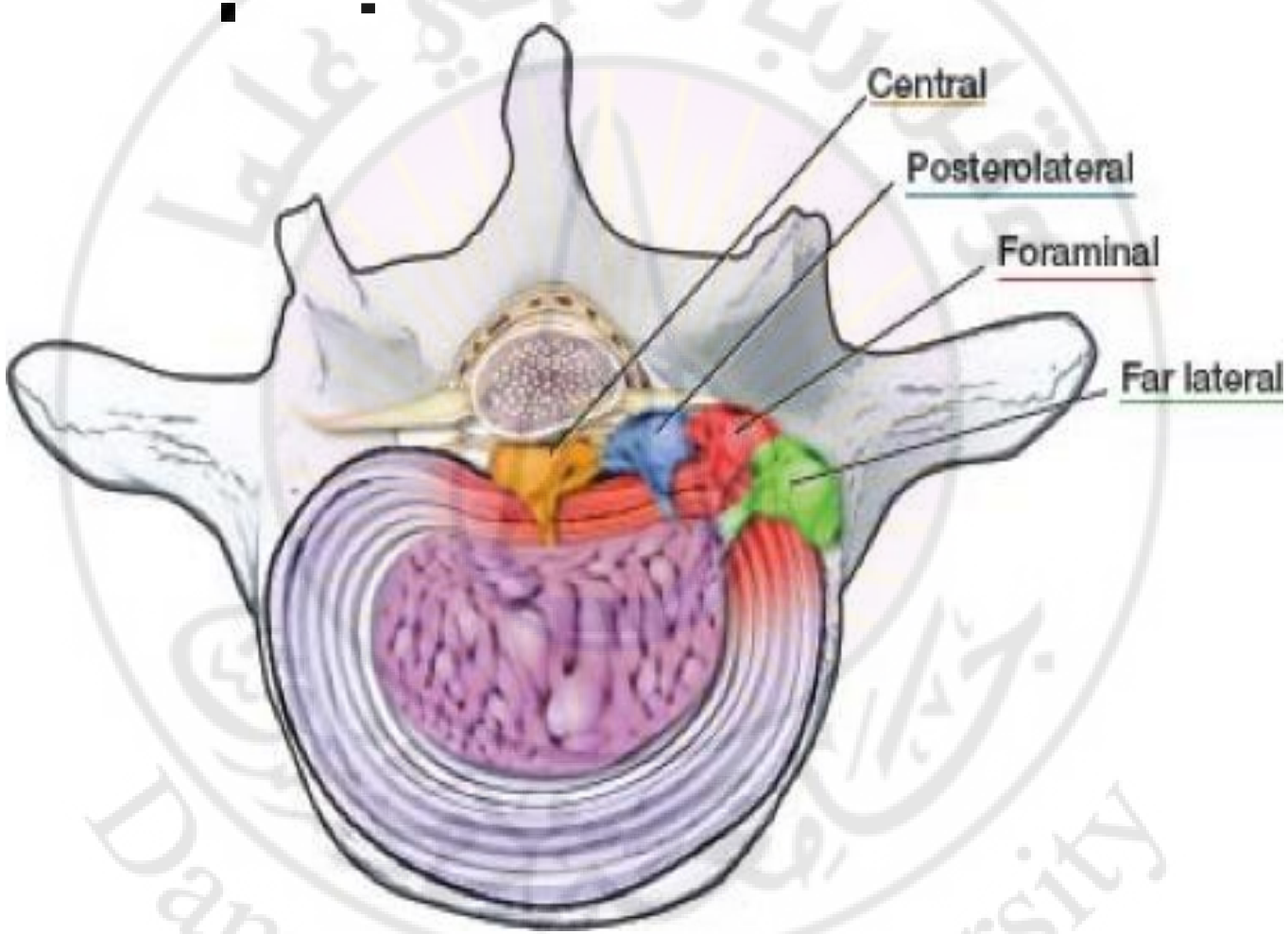


Nerve root lesions



Prolapsed intervertebral disc

Nerve root

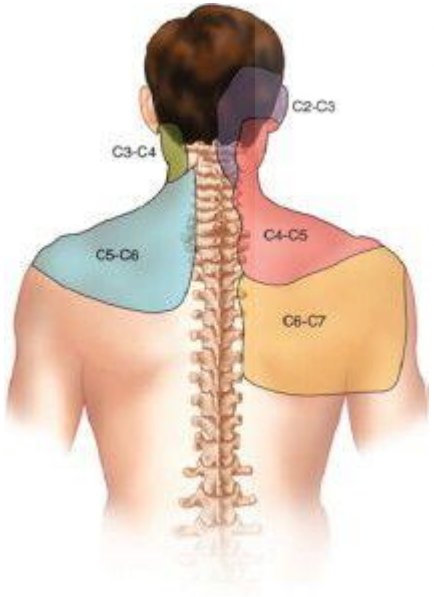


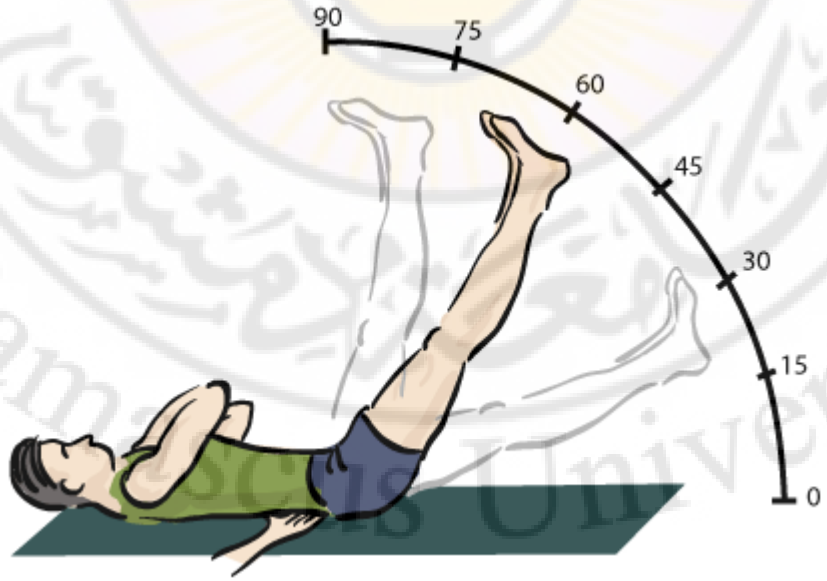
Prolapsed intervertebral disc

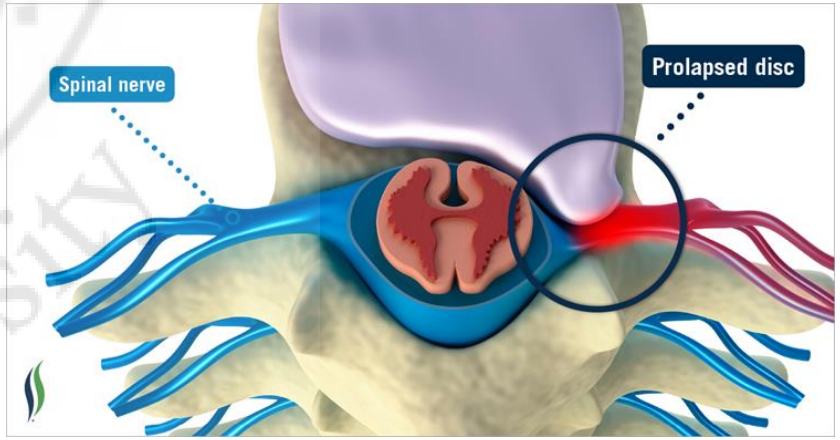
Nerve root lesions

The typical clinical features of a prolapsed intervertebral disc, regardless of the level, are

1. *Skeletal:*
- **pain, tenderness and limitation in the range of movement in the affected area of the spine;**
- **reduced straight leg raising on the side of the lesion, in the case of lumbar disc prolapses**







Nerve root lesions

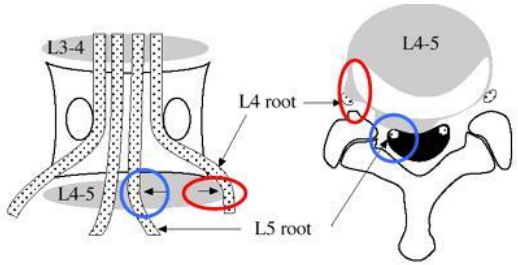
The typical clinical features of a prolapsed intervertebral disc, regardless of the level, are

2. *Neurological:*
- pain, sensory symptoms and sensory loss in the dermatome of the affected nerve root;
- lower motor neuron signs (weakness and wasting) in the myotome of the affected nerve root;
- loss of tendon reflexes of the appropriate segmental value;
- since most disc prolapses are posterolateral, these neurological features are almost always unilateral

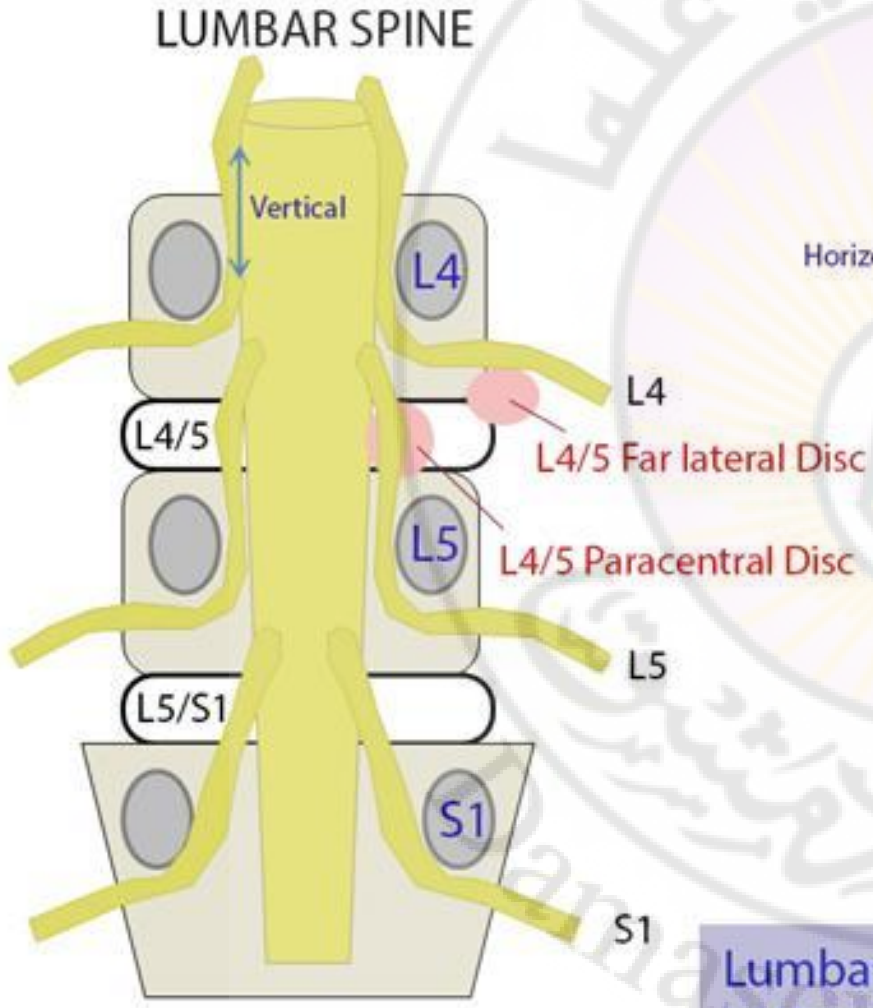
Nerve root lesions

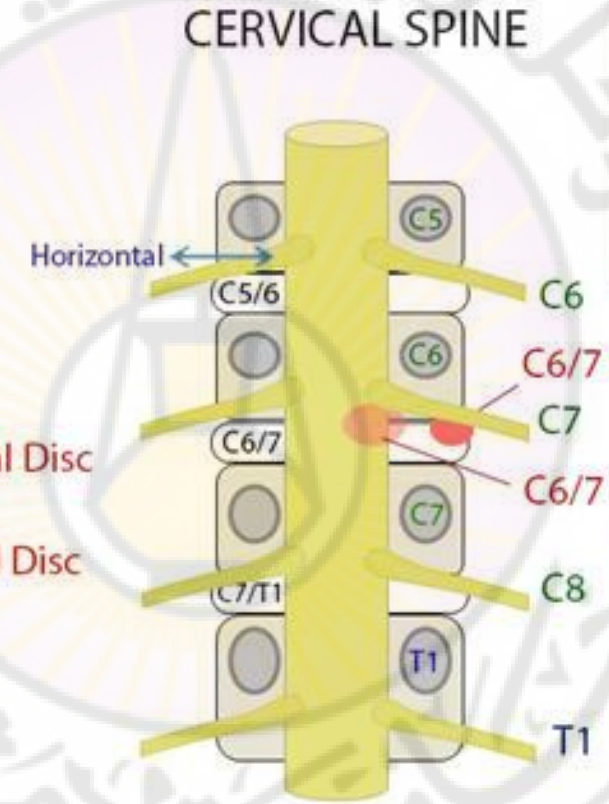
Common nerve roots to be compressed by prolapsed intervertebral discs:

In the arm	C5	In the leg	L4
	C6		L5
	C7		S1
	C8		



Nerve root lesions





Due to horizontal anatomy, both discs affect same nerve root in cervical spine, different than lumbar spine

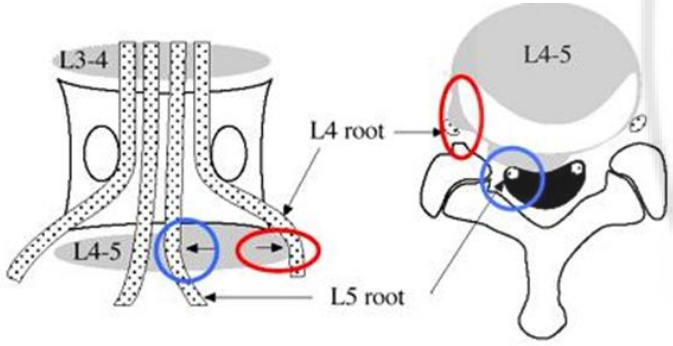
C8 and above Pedicle / Nerve Root MISMATCH

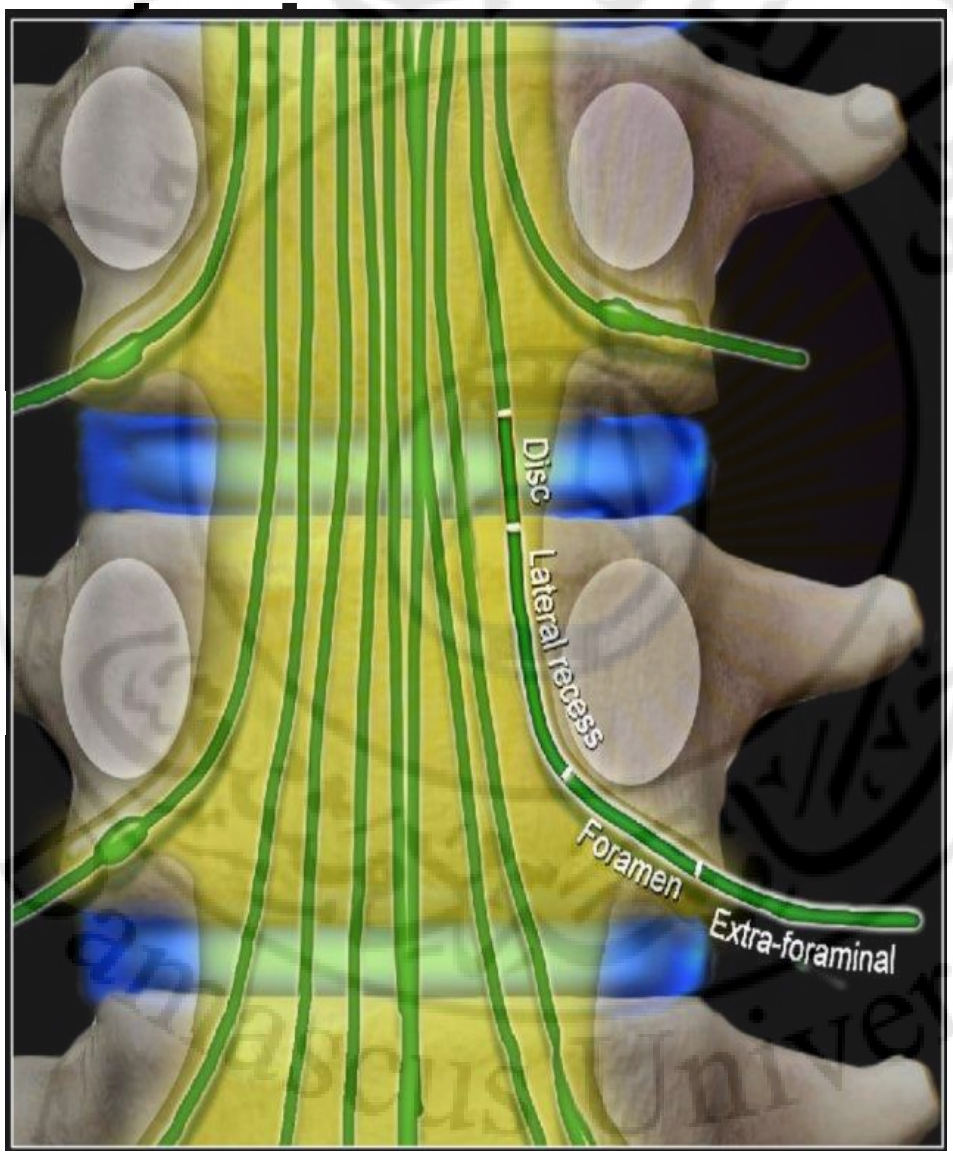
"Extra C8 Nerve Root (without C8 pedicle) allows transition from MISMATCH to MATCH

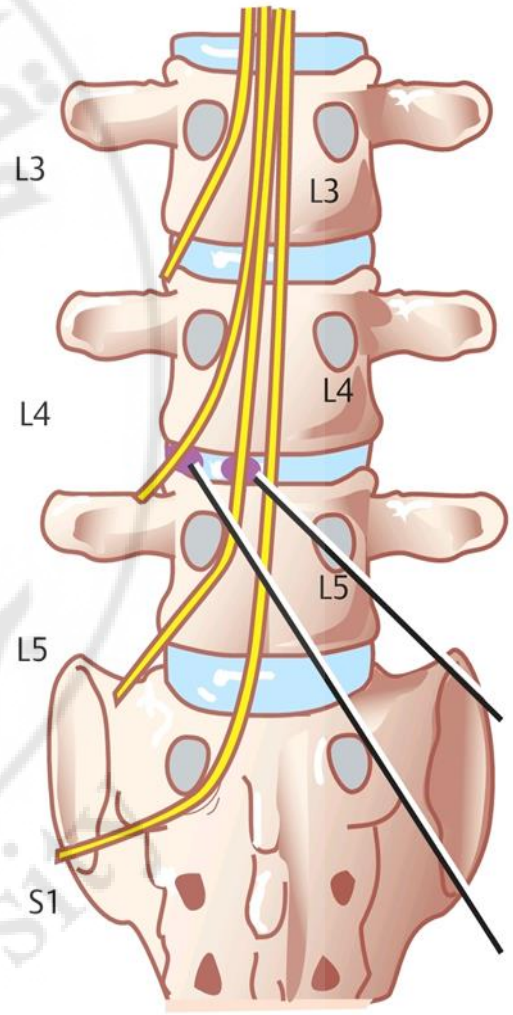
T1 and below Pedicle / Nerve Root MATCH

Lumbar Spine Pedicle/nerve Root MATCH

Nerve root







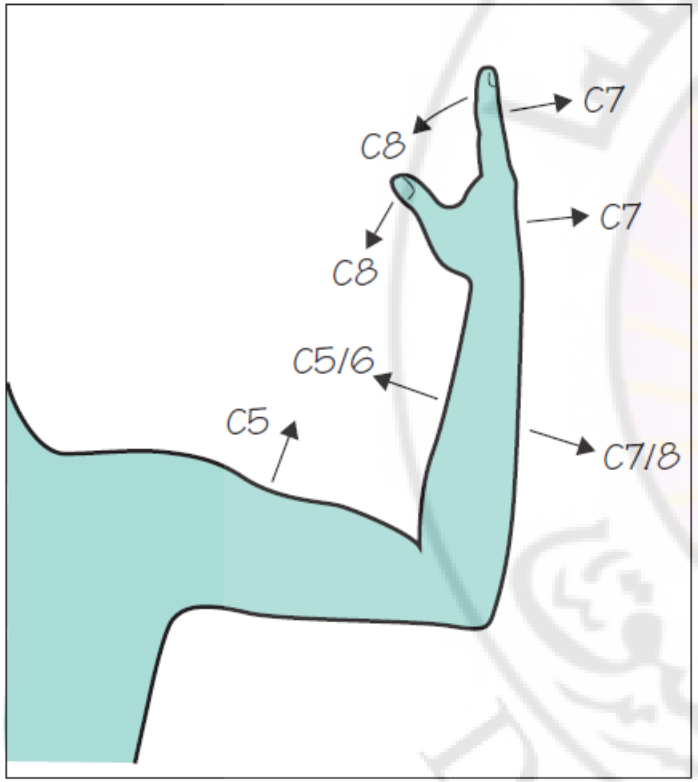
Note that the nerve root affected by a paracentral lumbar disc herniation corresponds in name to the vertebra below the disc. thus an L4–L5 disc herniation affects the l5 nerve root.

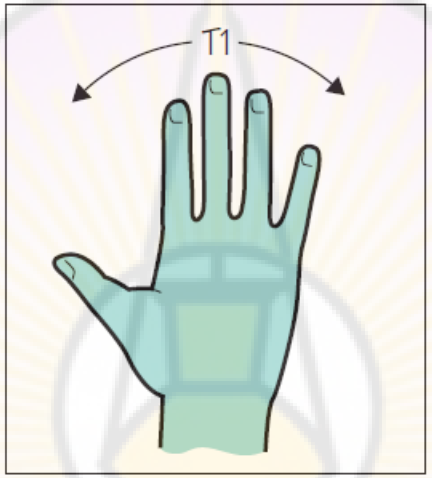
Note that a far lateral disc herniation affects the nerve root above the disc, (i.e., L4).

Paracentral disc herniation affects L5 nerve root (common)

Far lateral disc herniation affects L4 nerve root (uncommon)

Nerve root lesions

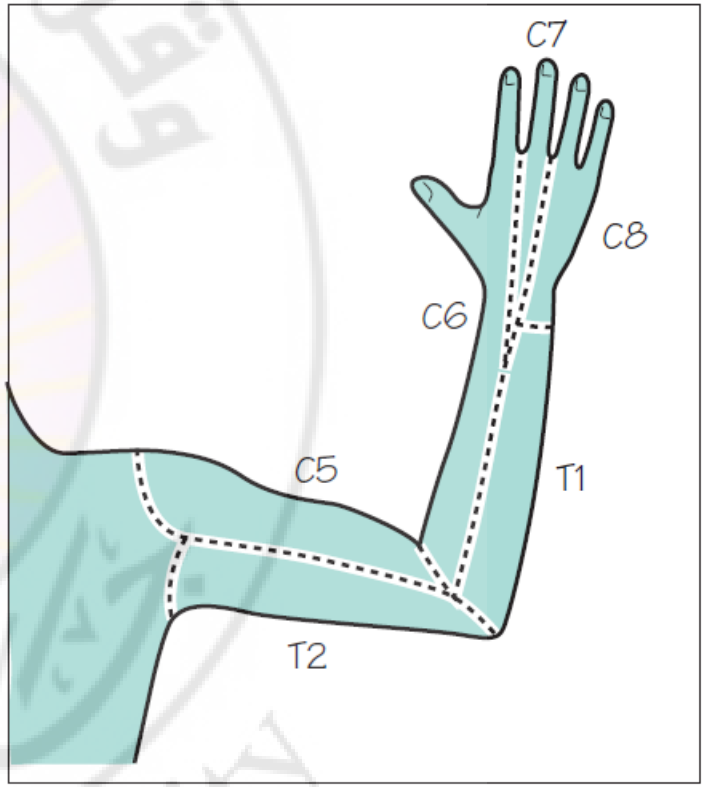




Biceps jerk C5/6

Triceps jerk C7/8

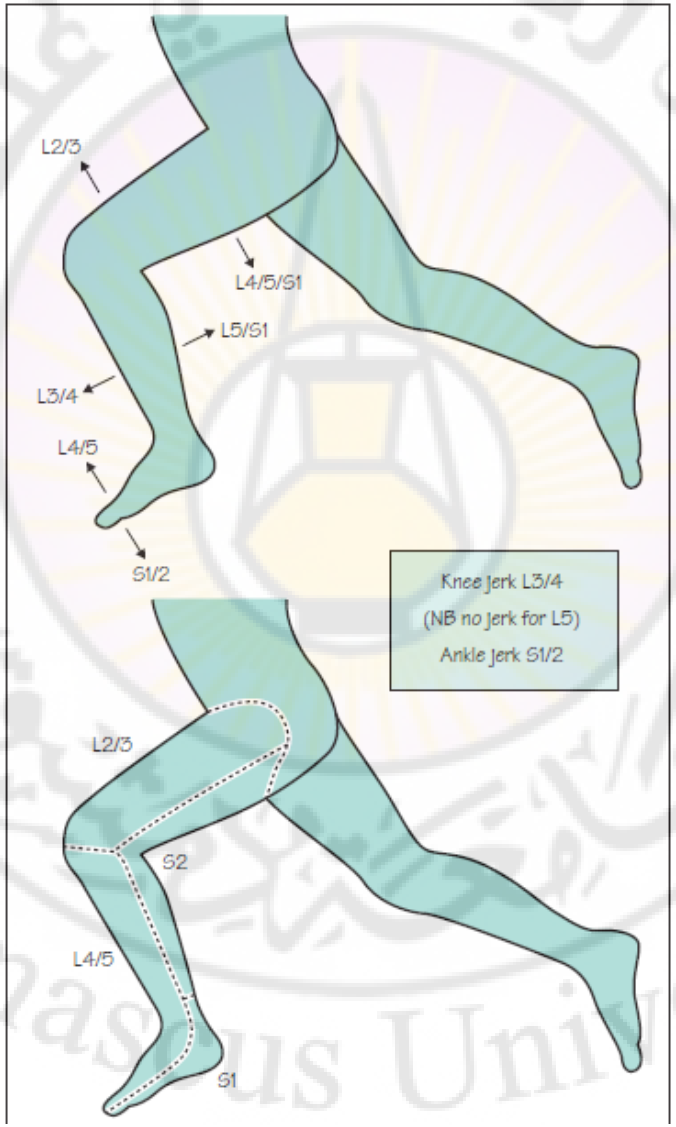
Supinator jerk C5/6



Segmental nerve supply to the upper limb, in terms of movements, tendon reflexes and skin sensation.

Nerve root le

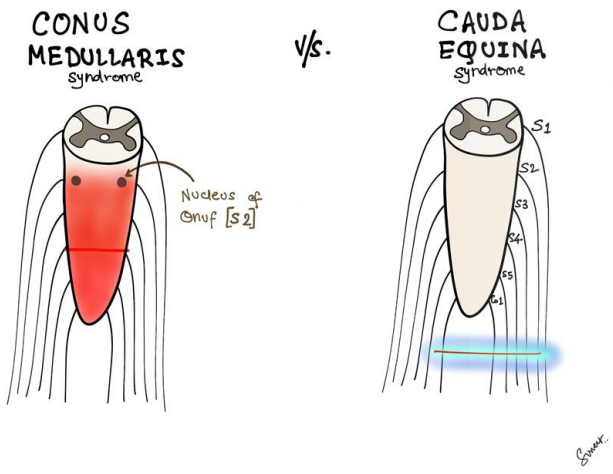
Segmental nerve supply to the lower limb, in terms of movements, tendon reflexes and skin sensation.

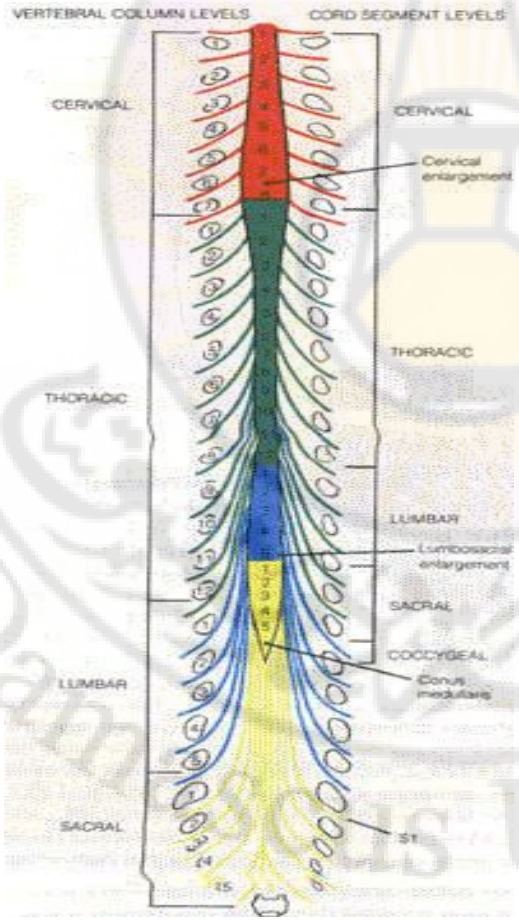


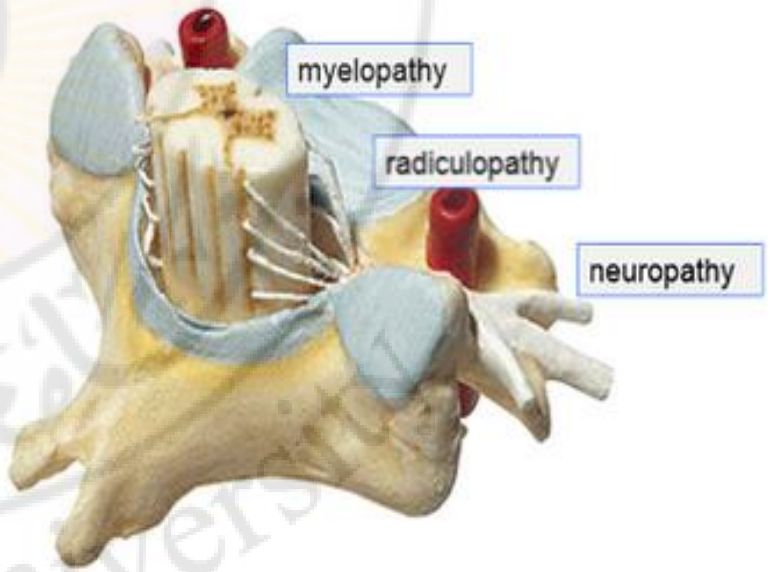
Nerve root lesions

There are four main intervertebral disc disease syndromes

- Myelopathy refers to spinal cord lesions.
- Radiculopathy refers to spinal nerve root lesions .
- Neuropathy refers to peripheral disease and includes plexopathies and mononeuropathies.



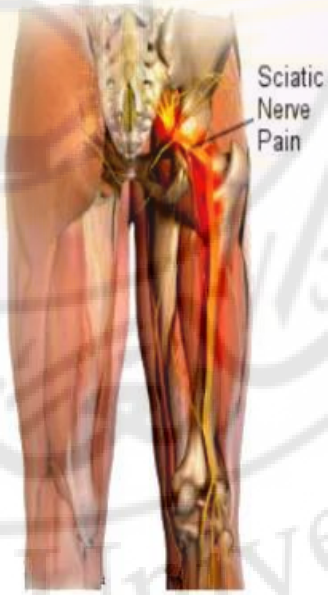


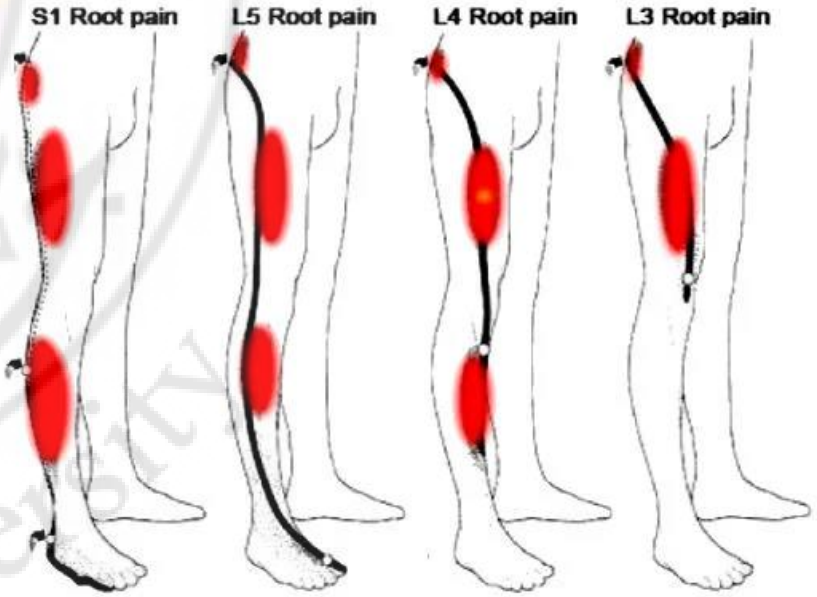


Nerve root lesions

There are four main intervertebral disc disease syndromes

1. The single, acute disc prolapse which is sudden, often related to unusually heavy lifting or exertion, painful and very incapacitating, often associated with symptoms and signs of nerve root compression, whether it affects the cervical or lumbar region.

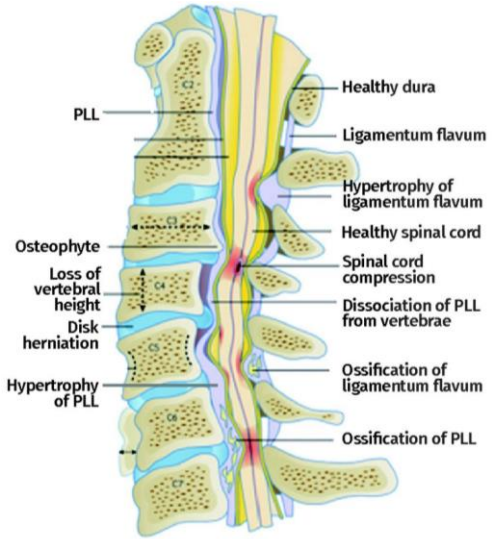


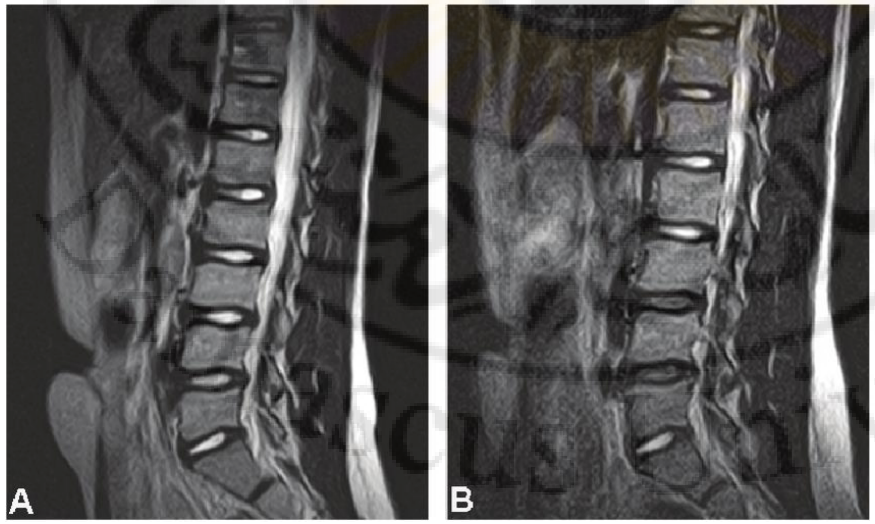


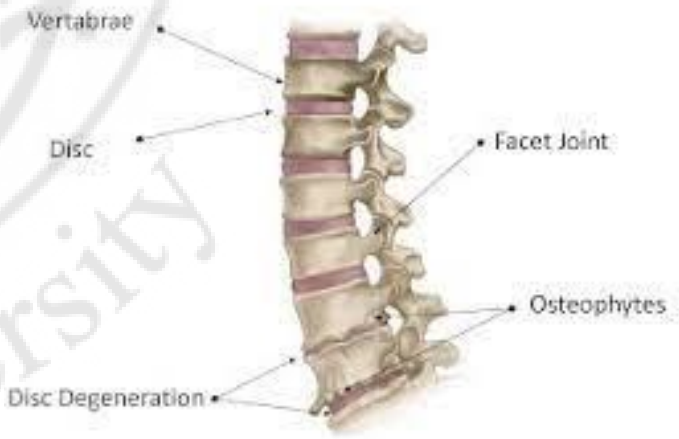
Nerve root lesions

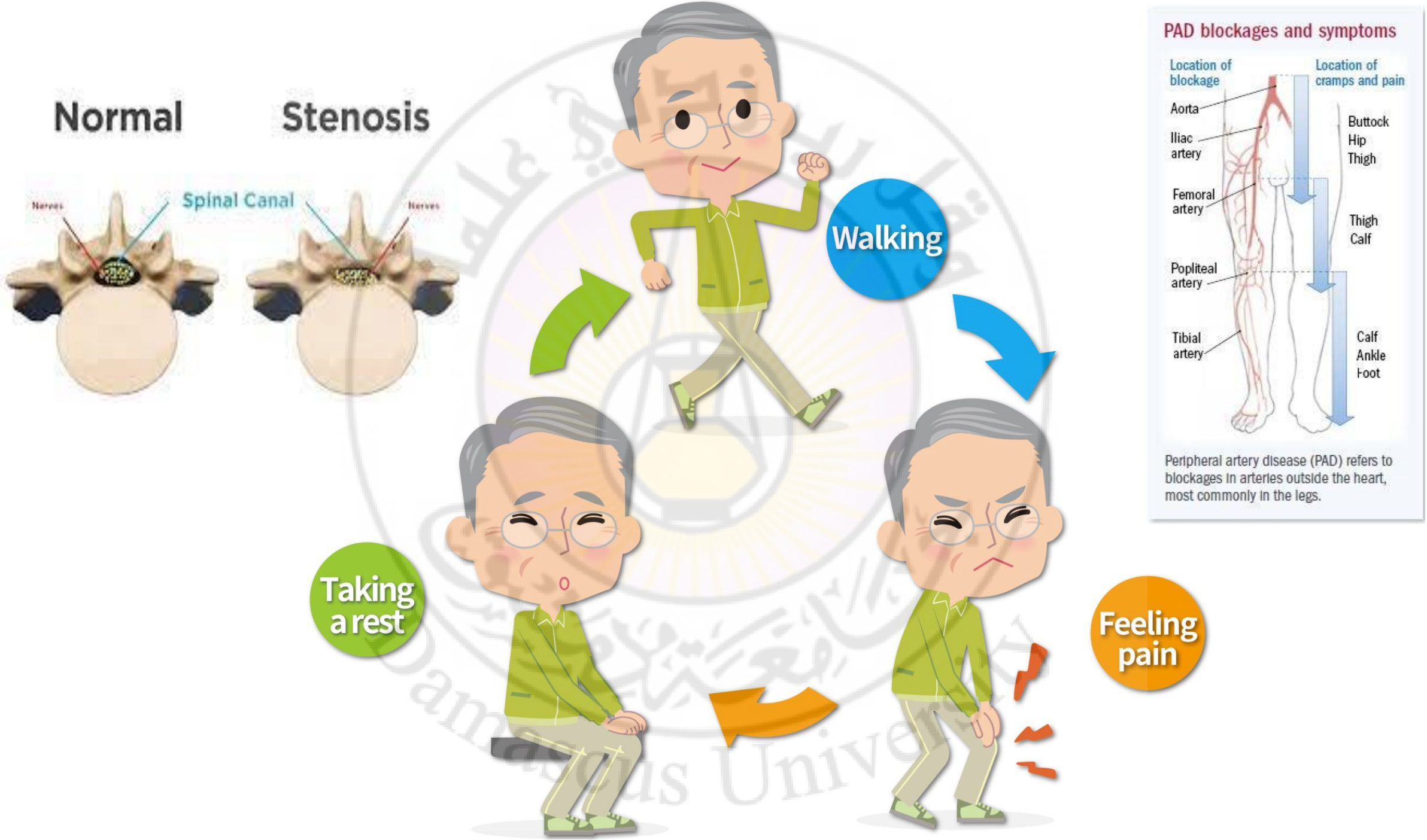
There are four main intervertebral disc disease syndromes

2. More gradually evolving, multiple-level disc herniation in association with osteo-arthritis of the spine. Disc degeneration is associated with osteophyte formation, not just in the main intervertebral joint between body and body, but also in the intervertebral facet joints. Osteoarthritic changes in the intervertebral facet joint may further encroach upon the space available for the emerging spinal nerve in the intervertebral foramen. This is the nature of nerve root involvement in cervical and lumbar spondylosis







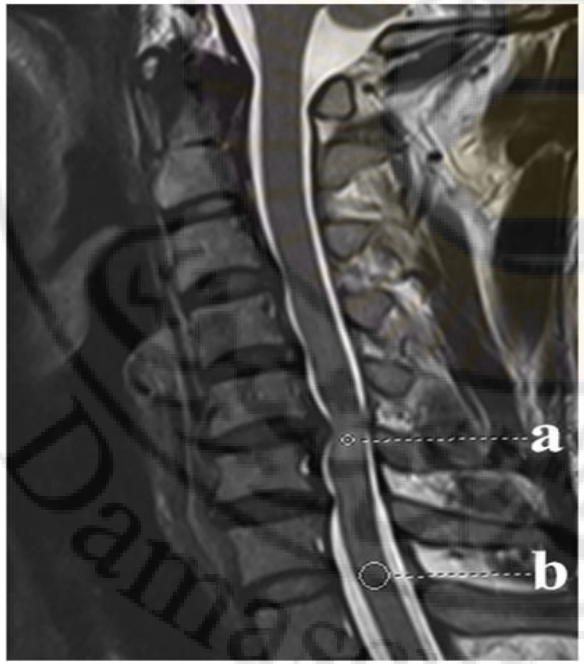

Normal
Stenosis
Nerves
Spinal Canal
Nerves
Walking
Feeling pain
Taking a rest
PAD blockages and symptoms
Location of blockage
Location of cramps and pain
Aorta
Iliac artery
Femoral artery
Popliteal artery
Tibial artery
Buttock
Hip
Thigh
Thigh
Calf
Calf
Ankle
Foot
Peripheral artery disease (PAD) refers to blockages in arteries outside the heart, most commonly in the legs.

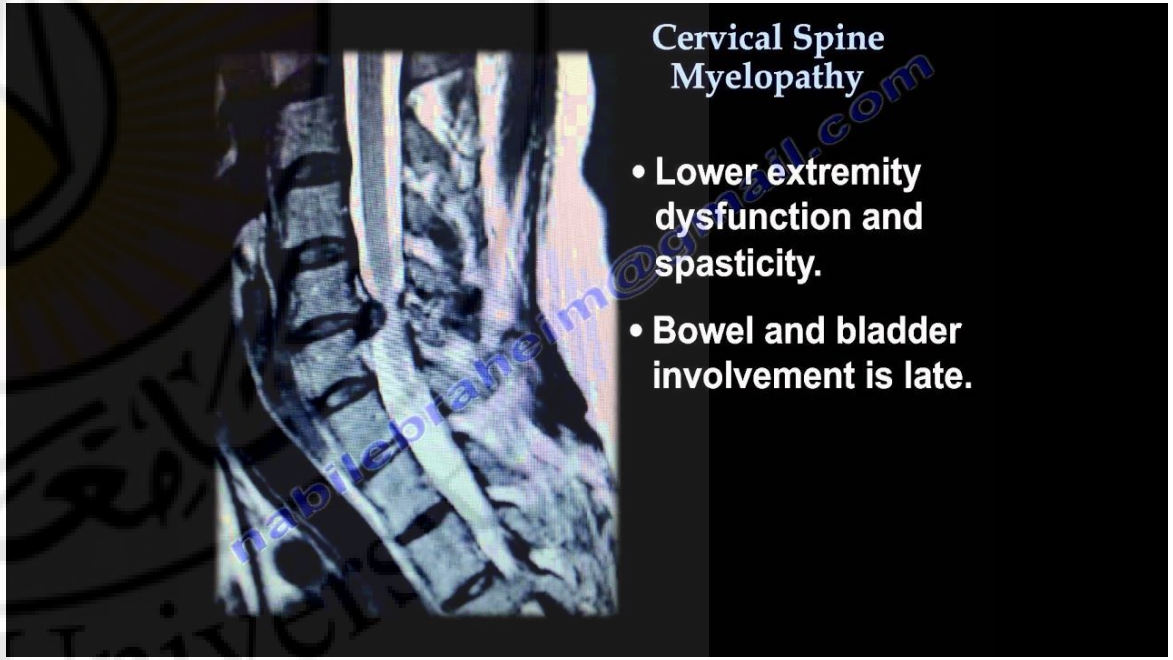

Spinal stenosis
Symptoms worsen
with lumbar extension
Leaning forward relieves
pressure, lessening symptoms

Nerve root lesions

There are four main intervertebral disc disease syndromes

3. Cervical myelopathy when 1, or more commonly 2 above, causes spinal cord compression in the cervical region. This is more likely in patients with a constitutionally narrow spinal canal.





Nerve root lesions

There are four main intervertebral disc disease syndromes

3. Cervical myelopathy when 1, or more commonly 2 above, causes spinal cord compression in the cervical region. This is more likely in patients with a constitutionally narrow spinal canal.

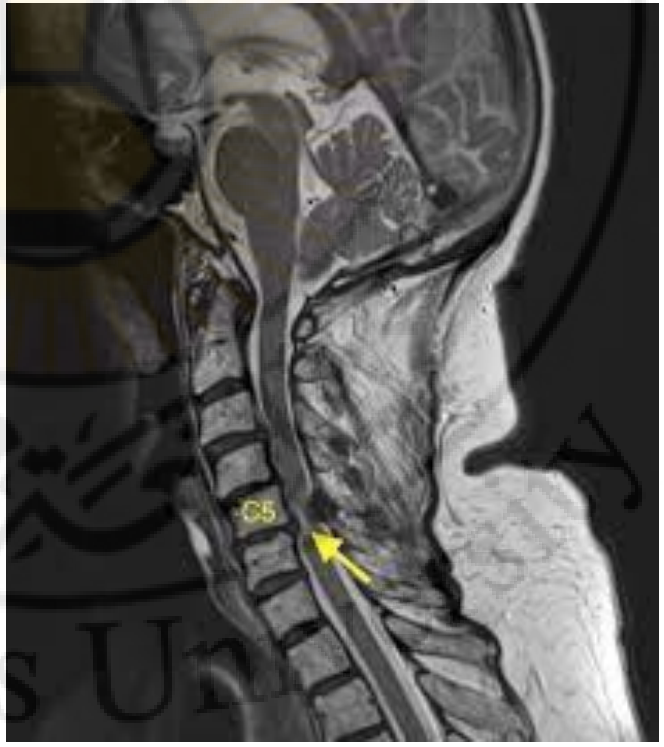
Cervical Myelopathy

Description | impingement on the spinal cord due to a vertebral canal obstruction in the C-spine

- **Risk Factors - Anything that narrows vertebral canal**
  - Cervical spondylosis
  - Age ≥ 50-60
  - Neck trauma
    - MVA
    - Sports injury
  - RA (C1-C2 interval)

S/S

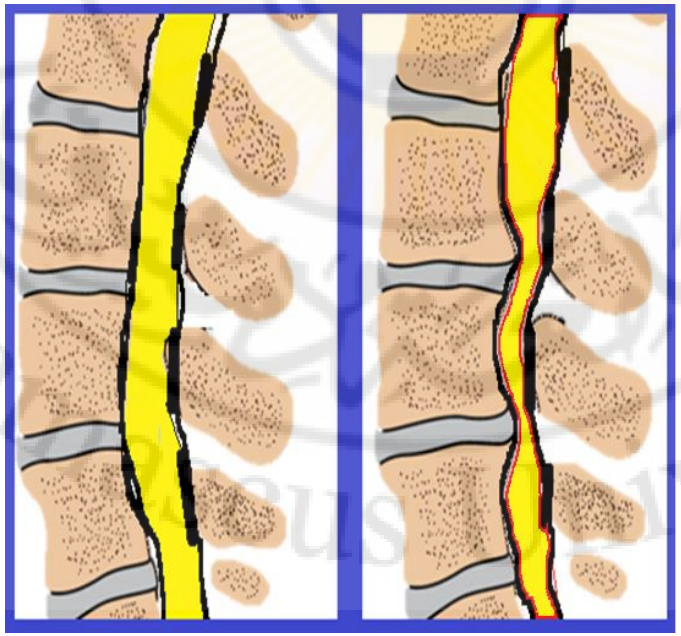
- Neck and upper extremity pain
- Weakness and sensory impairments
  - UE > LE
- LMN signs at the level of lesion (weakness and hyporeflexia)
- UMN signs below the level of lesion (spasticity & hyperreflexia)
  - UMN Signs (Hoffman's, clonus, and Babinski reflexes)
- Parasthesia with weakness and wasting of the hands
- Gait disorders (wide based, ataxia)
- Bowel and bladder dysfunction
- Loss of deep touch, vibration, and joint position sense (posterior column involvement)
- Lhermitte's sign



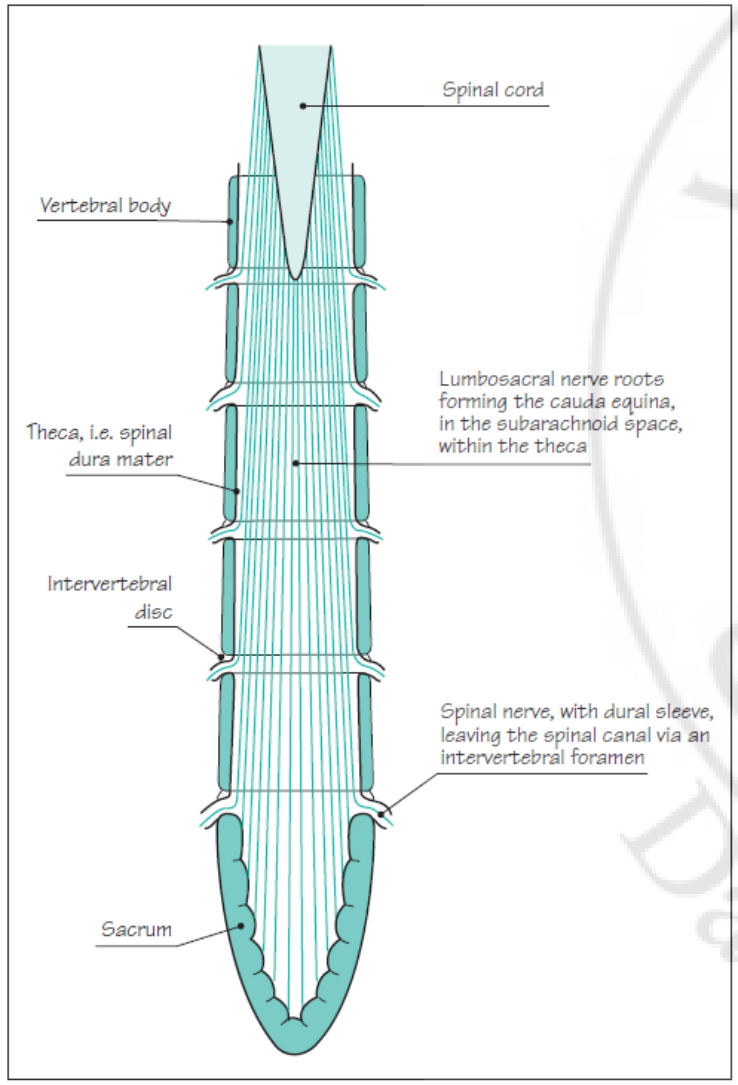
Nerve root lesions

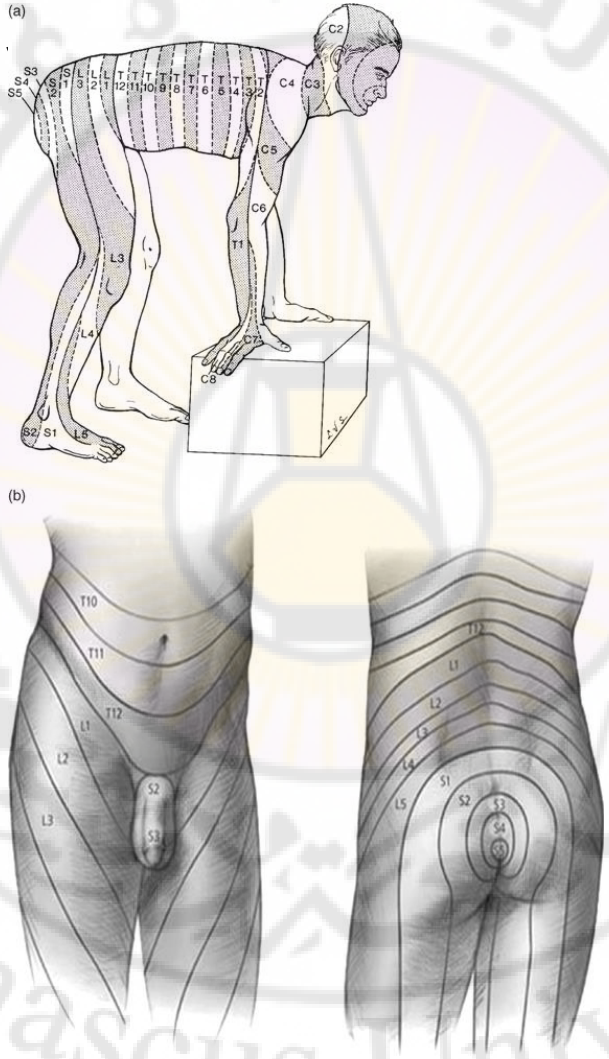
There are four main intervertebral disc disease syndromes

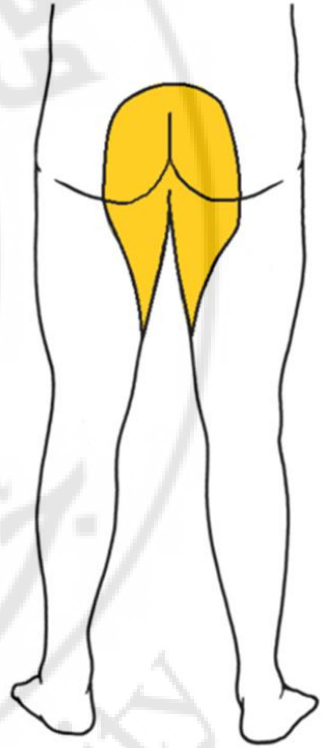
4. Cauda equina compression at several levels due to lumbar disc disease and spondylosis, often in association with a constitutionally narrow canal, may produce few or no neurological problems when the patient is at rest. The patient may develop sensory loss in the legs or weakness on exercise. This syndrome is not common, its mechanism is ill-understood, and it tends to be known as 'intermittent claudication of the cauda equina'.

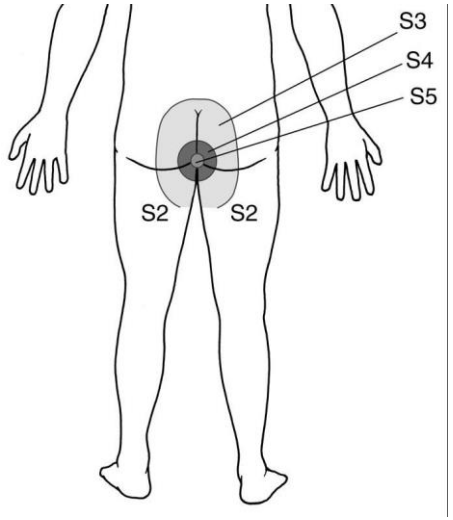


Nerve root le

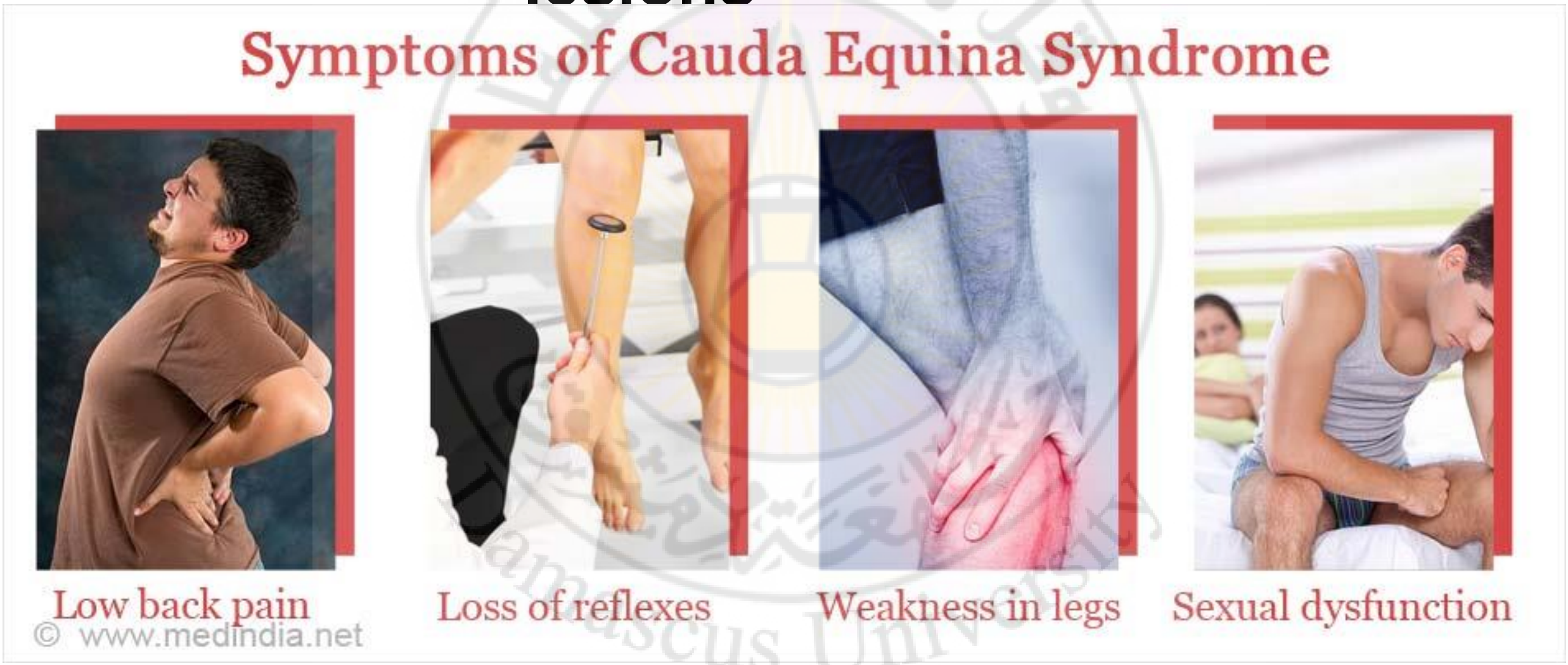








Nerve root lesions

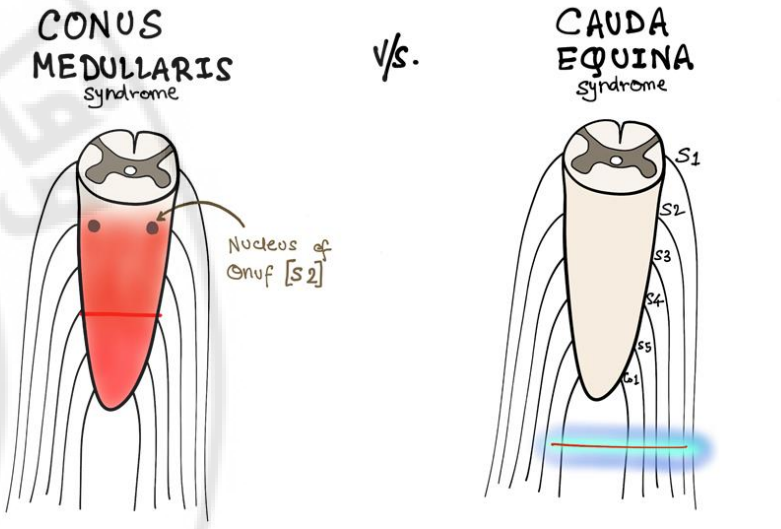


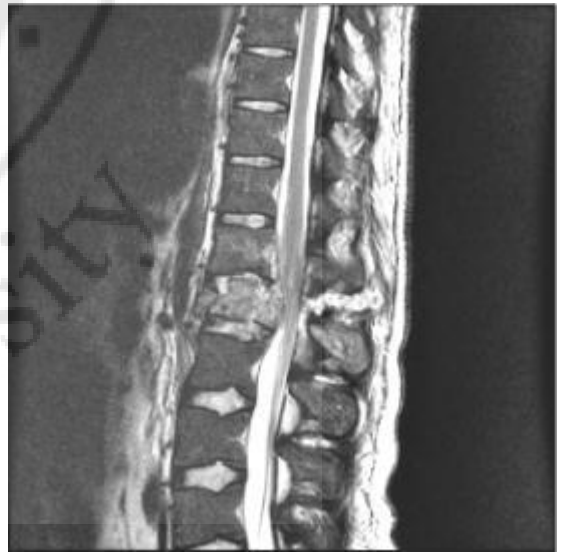
Nerve root lesions

There is another intervertebral disc disease syndromes

Conus Medullaris vs. Cauda Equina Lesion

Finding	Conus	CE
Pain	Uncommon	Common
Reflexes	Increased	Decreased
Bowel/bladder	Common	Uncommon

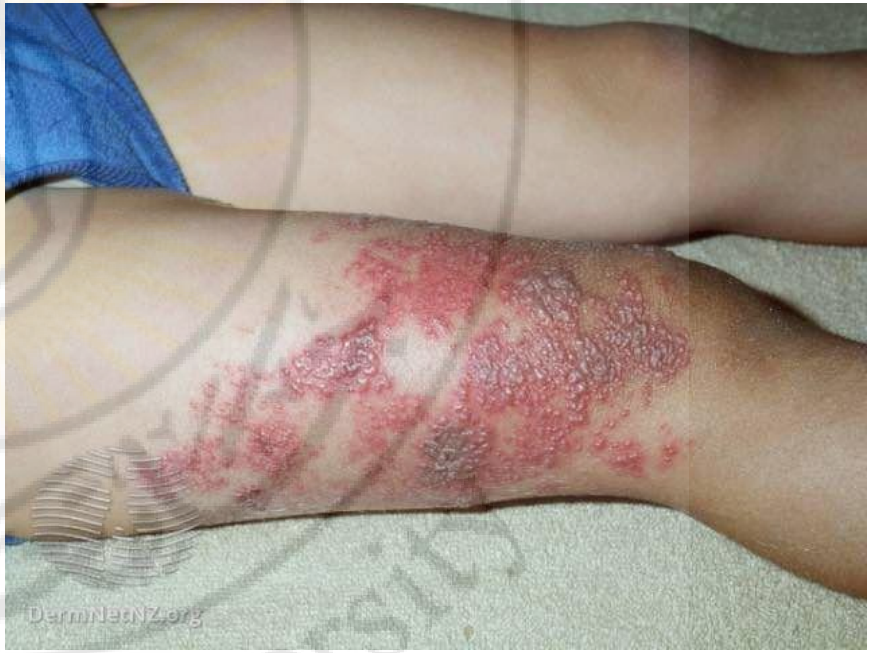




Nerve root lesions

Herpes zoster

The painful vesicular eruption of shingles of dermatome distribution is well known. Pain may precede the eruption by a few days, secondary infection of the vesicles easily occurs, and pain may occasionally follow the rash on a long-term basis (postherpetic neuralgia).



Nerve root lesions

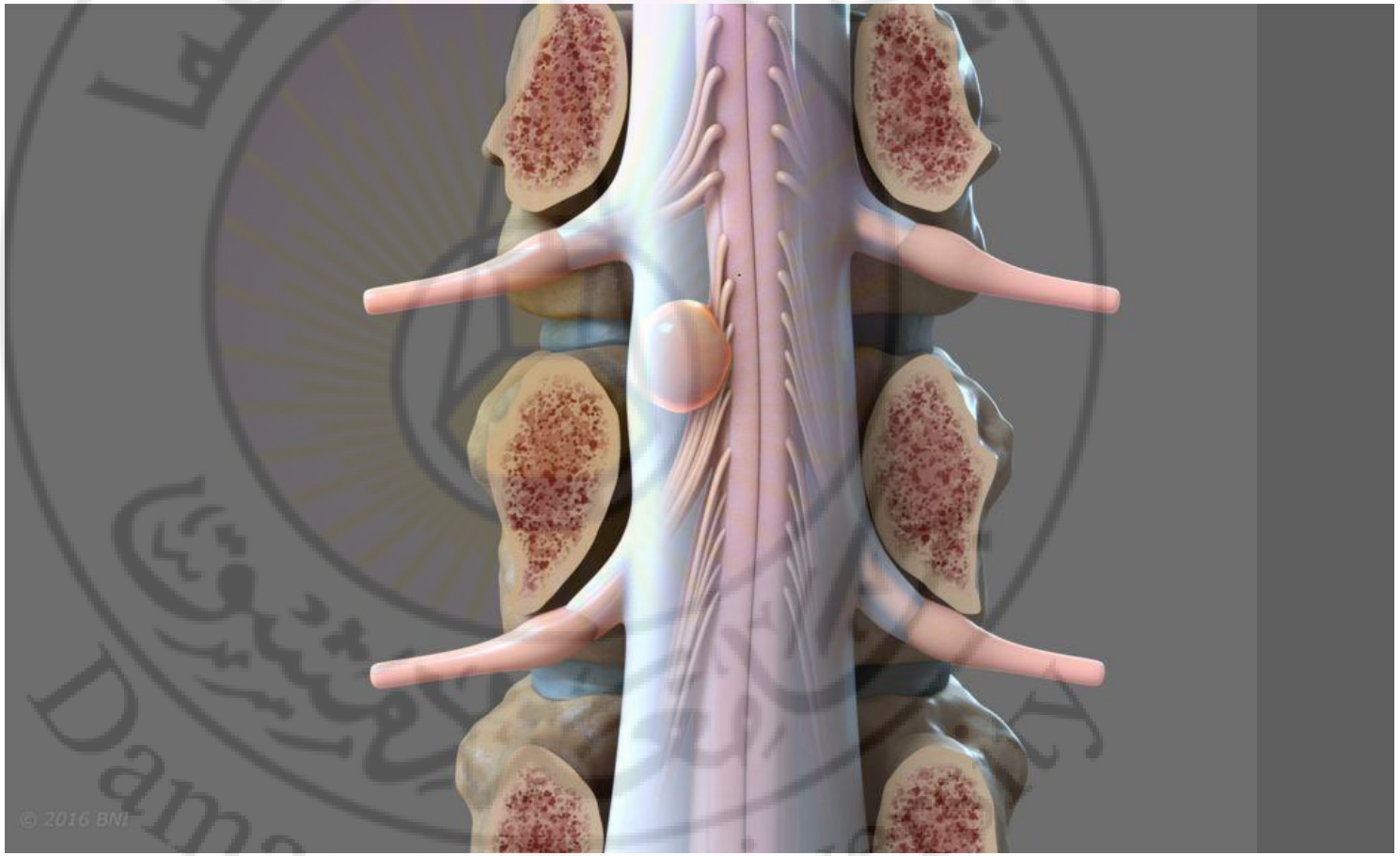
Spinal tumours

Types of spinal tumors?

- Where the tumor's located along the spine (cervical, thoracic, lumbar or sacrum).
- Where the tumor's located within the spinal column (intradural-extramedullary, intramedullary or extradural).
- If the tumor began in the spine (primary spinal tumor) or is the result of metastasis from cancer in another area of your body (secondary spinal tumor).
- If the tumor is benign (noncancerous) or malignant (cancerous).

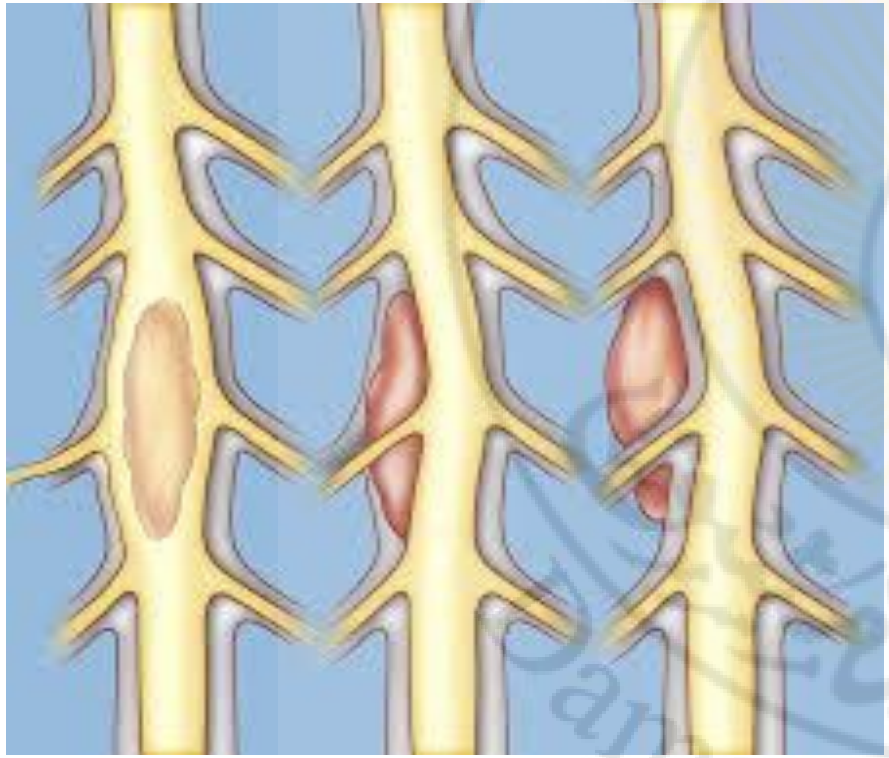
Nerve root lesions

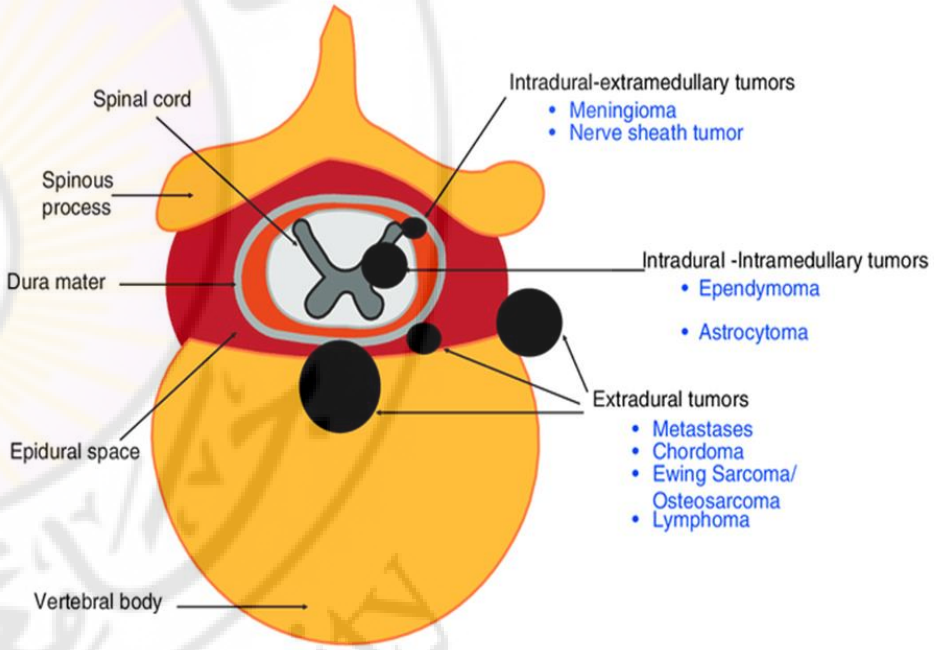
Spinal tumours



Nerve root lesions

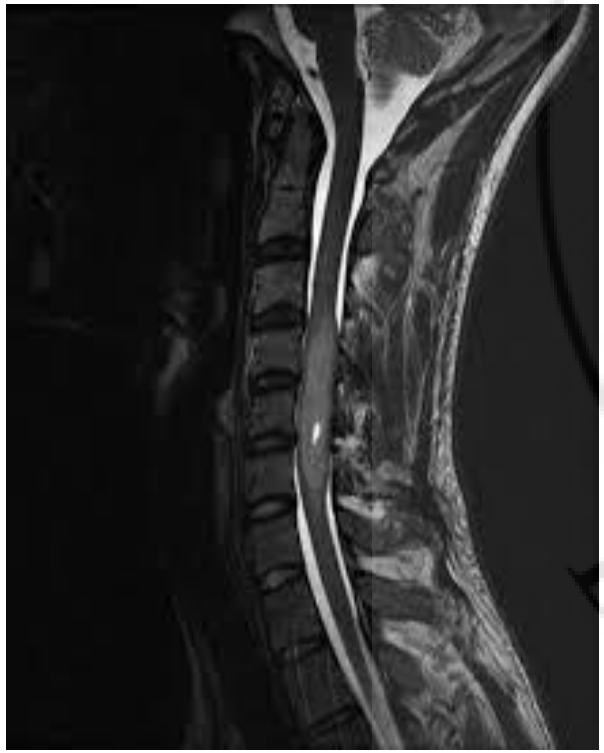
Spinal tumours



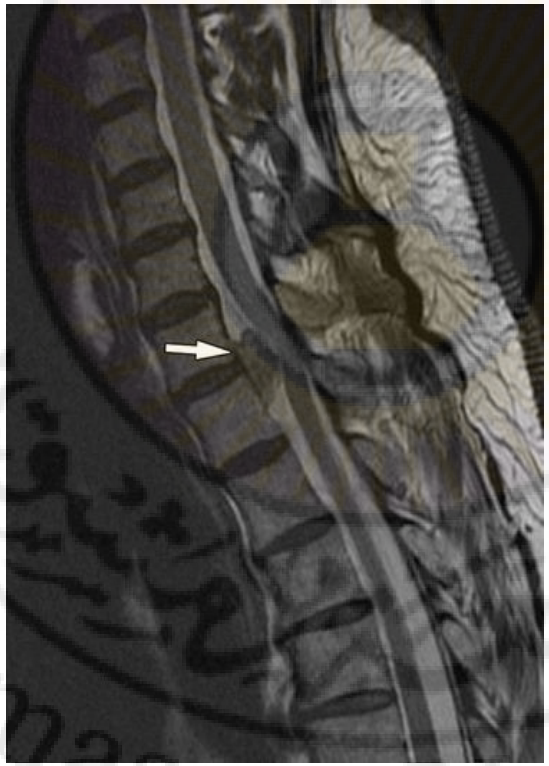


Nerve root lesions

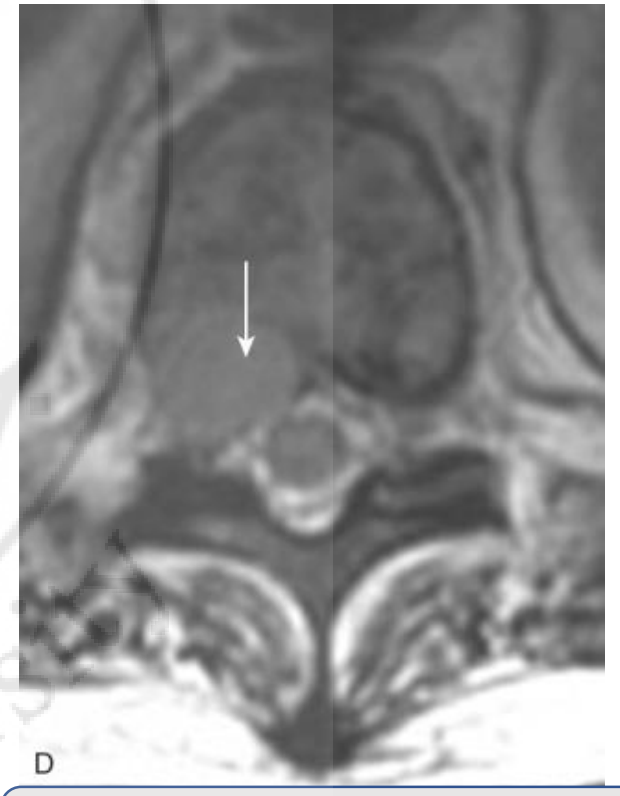
Spinal tumours



Intramedullary spinal cord astrocytomas



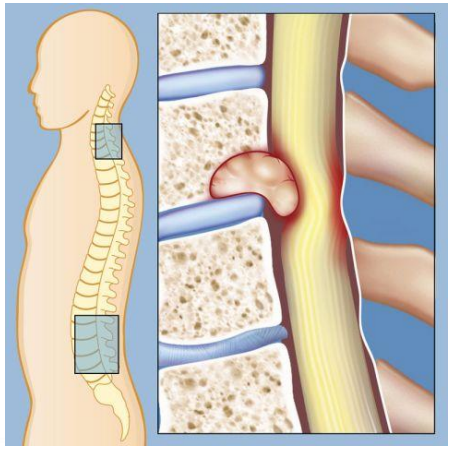
Intradural Extramedullary Spinal Meningioma

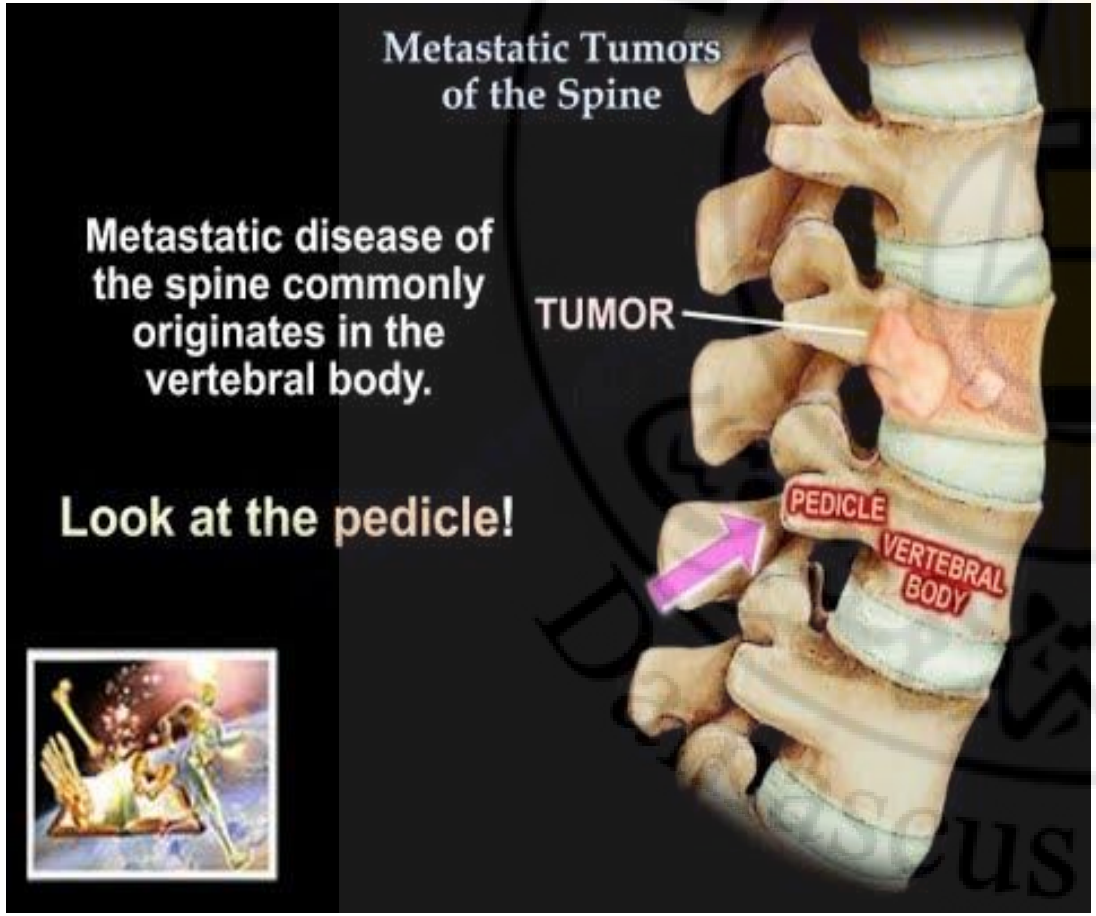


Extradural Spinal Tumors Metastatic Disease

Nerve root lesions

Spinal tumours





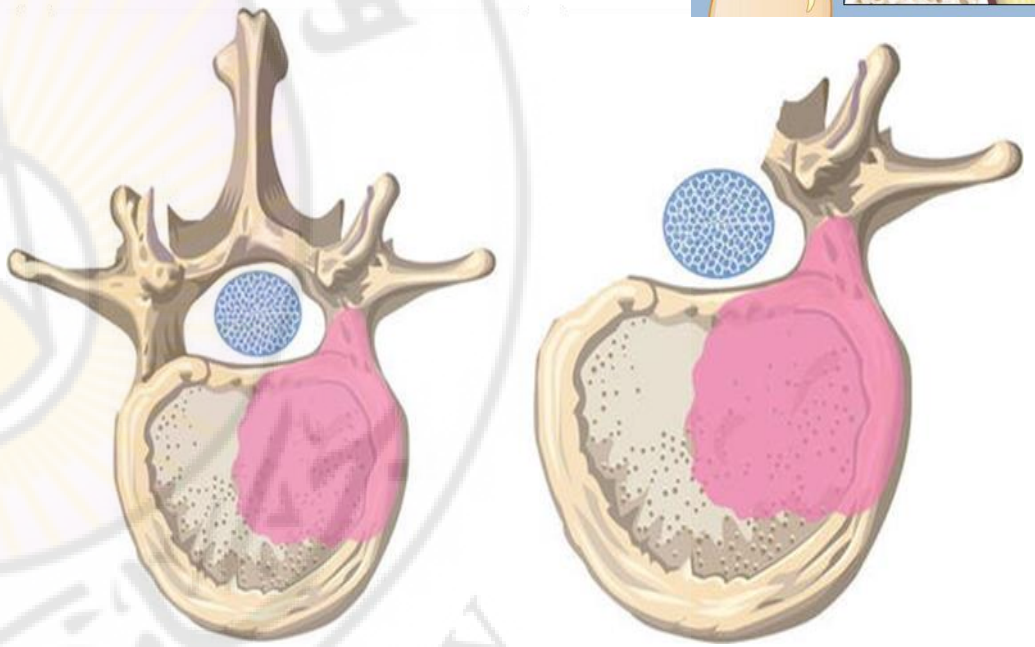
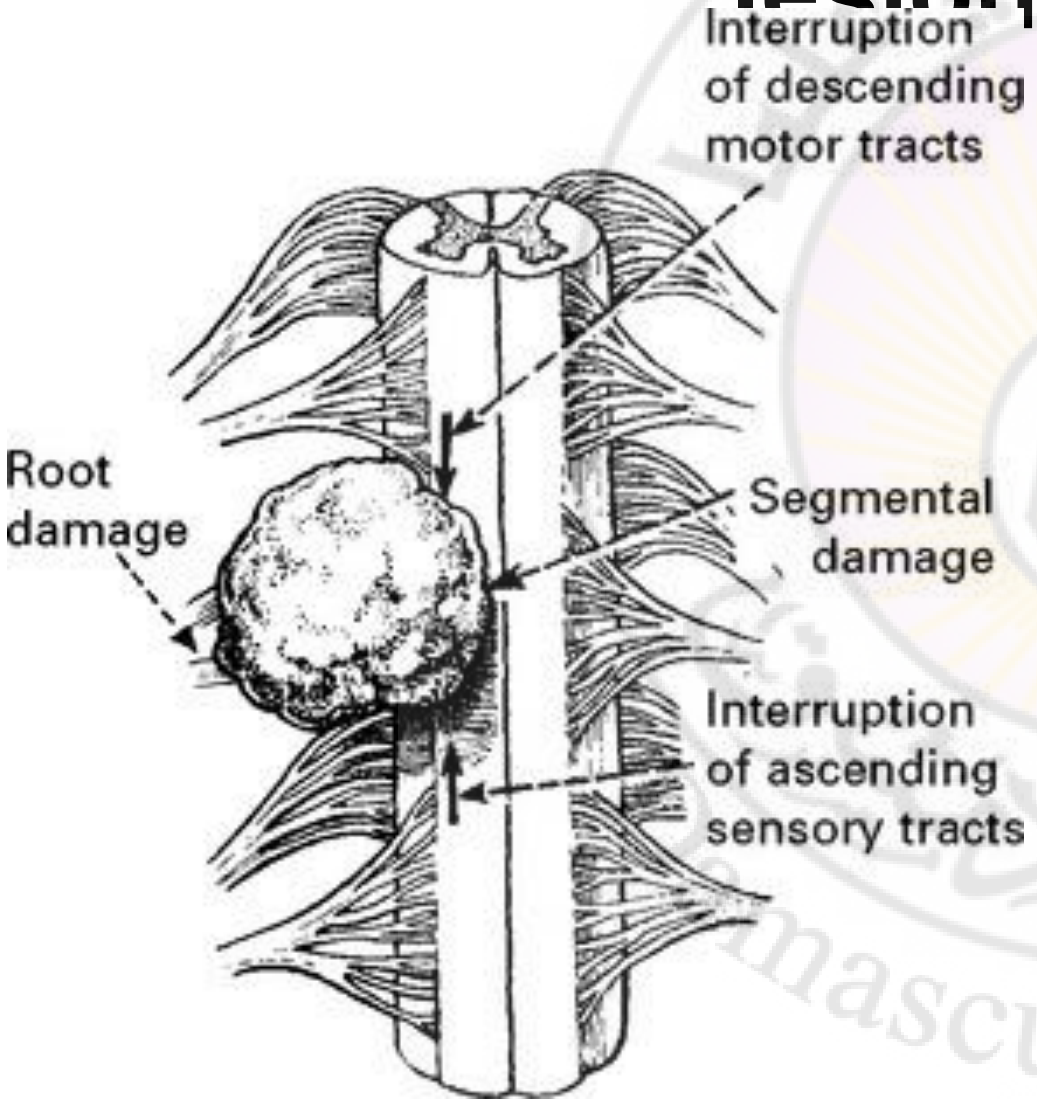
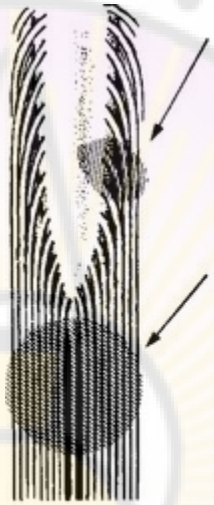


Illustration of tumor involvement of one pedicle. b The non affected, healthy posterior elements are resected including the pedicle in order to create a corridor to release the dural tube

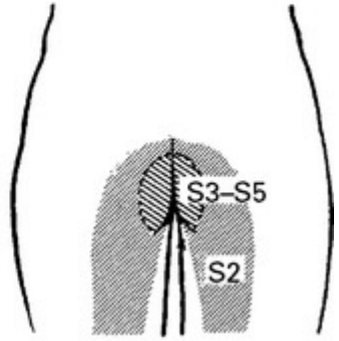
Nerve root lesions



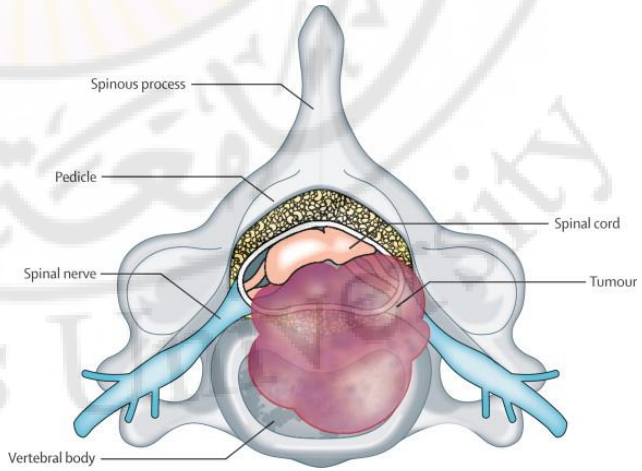


Root or segmental lesions may involve the upper part of the cauda equina and produce root/segmental and long tract signs as described on the previous page, e.g. an expanding proximal L4 root lesion causes weakness and wasting of the foot dorsiflexors, sensory deficit over the inner calf, an increased ankle jerk and an extensor plantar response. Bladder involvement tends to occur late.

The lower sacral roots are involved early, producing loss of motor and sensory bladder control with detrusor paralysis. Overflow incontinence ensues. Impotence and faecal incontinence may be noted. A l.m.n. weakness is found in the muscles supplied by the sacral roots (foot plantarflexors and evertors), the ankle jerks are absent or impaired and a sensory deficit occurs over the '*saddle*' area.

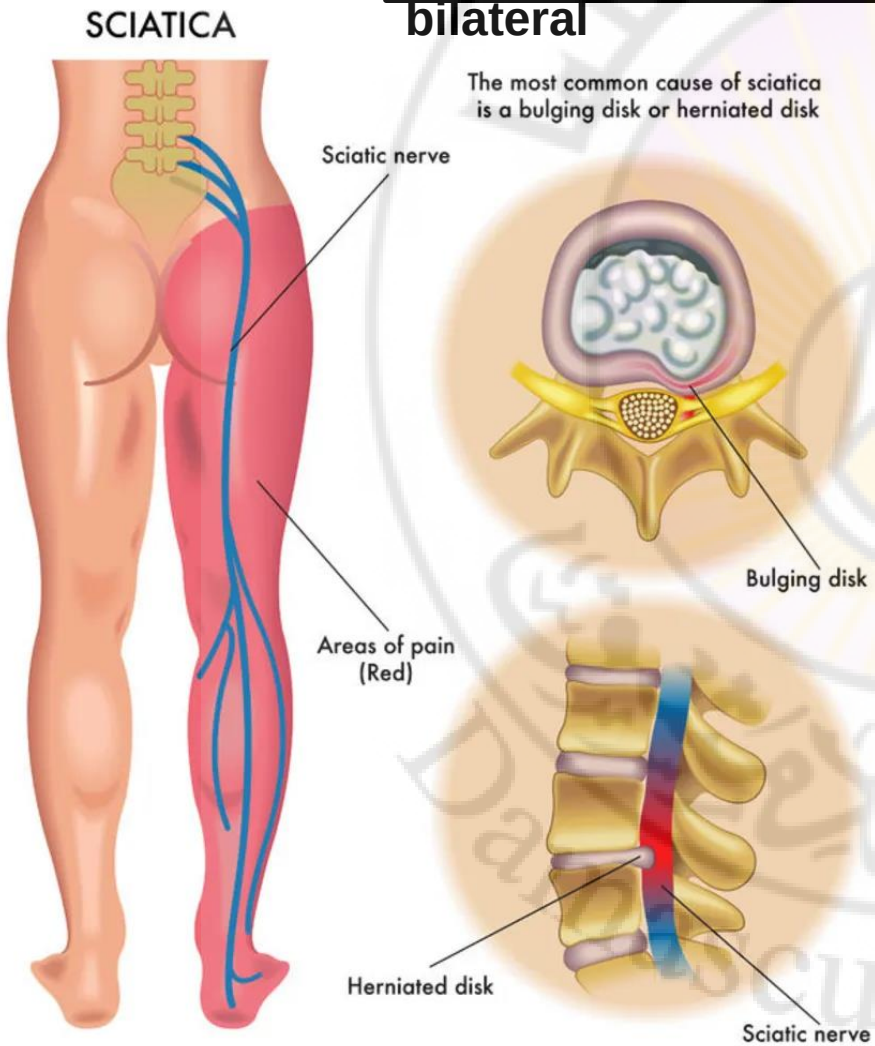


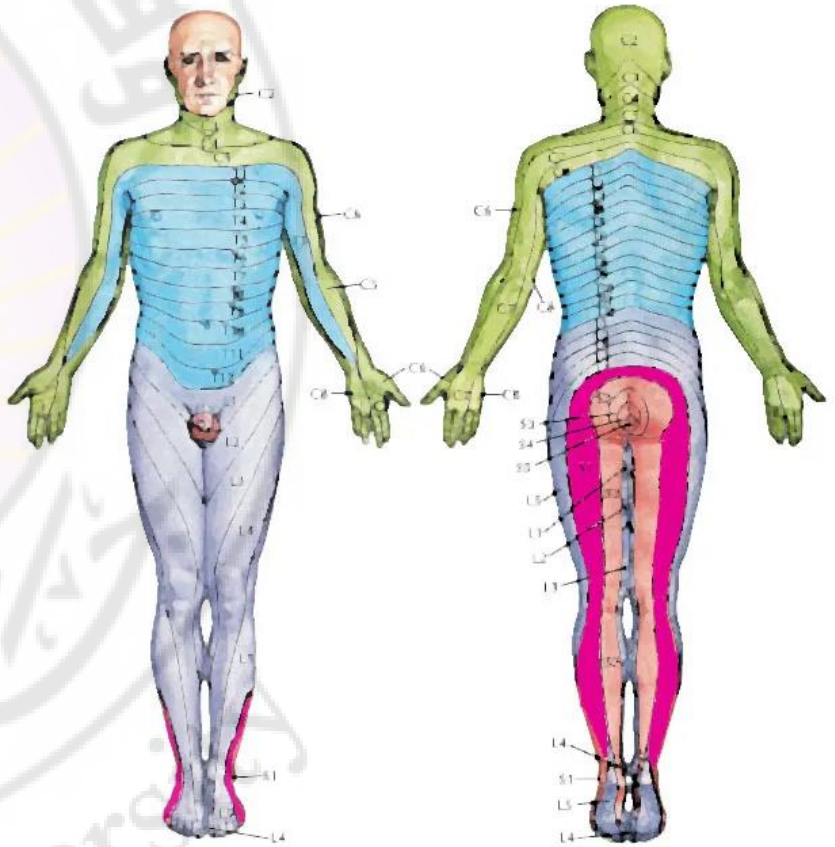
'Saddle' area.



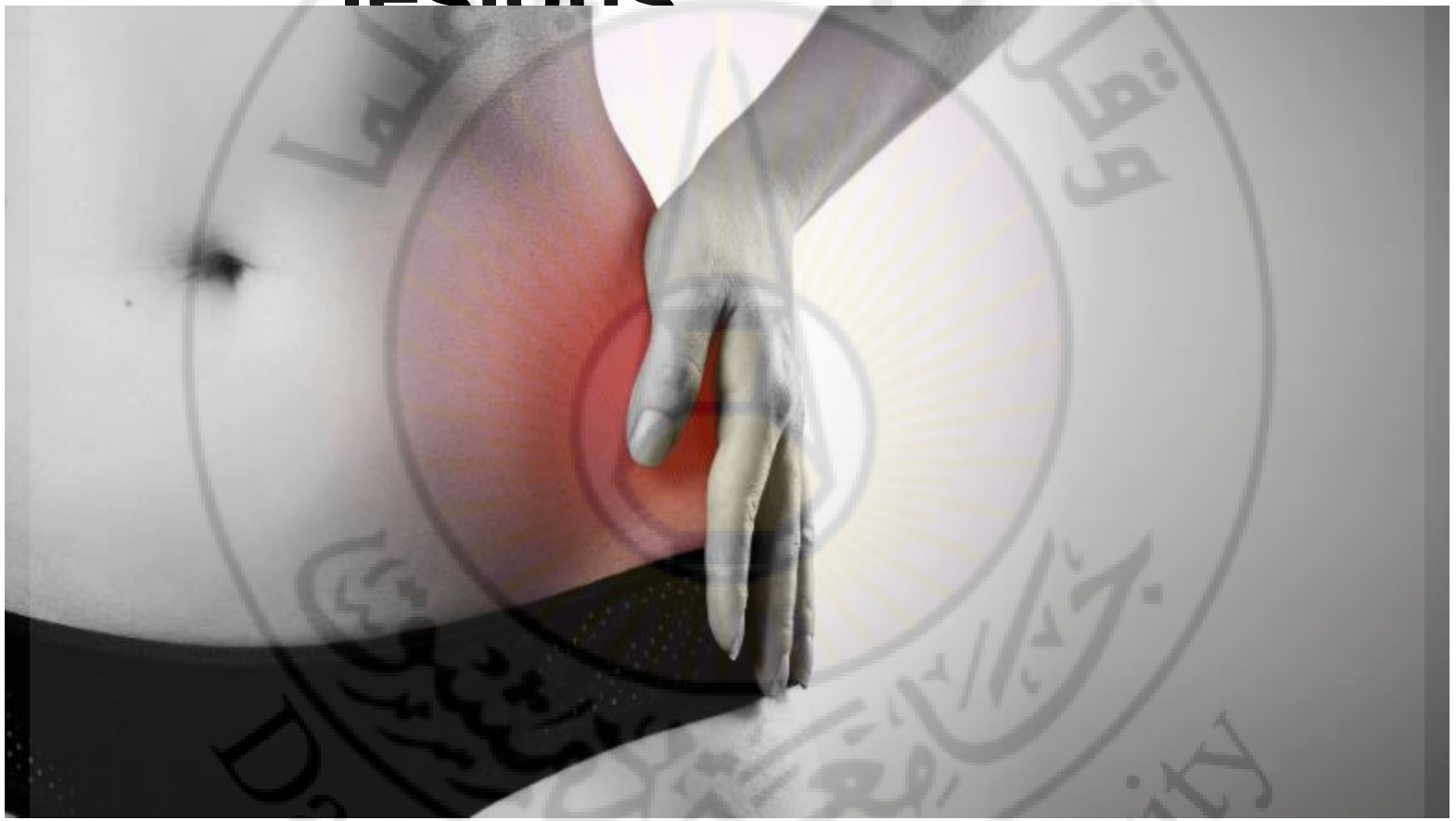
Nerve root

The root pain may be either unilateral or bilateral



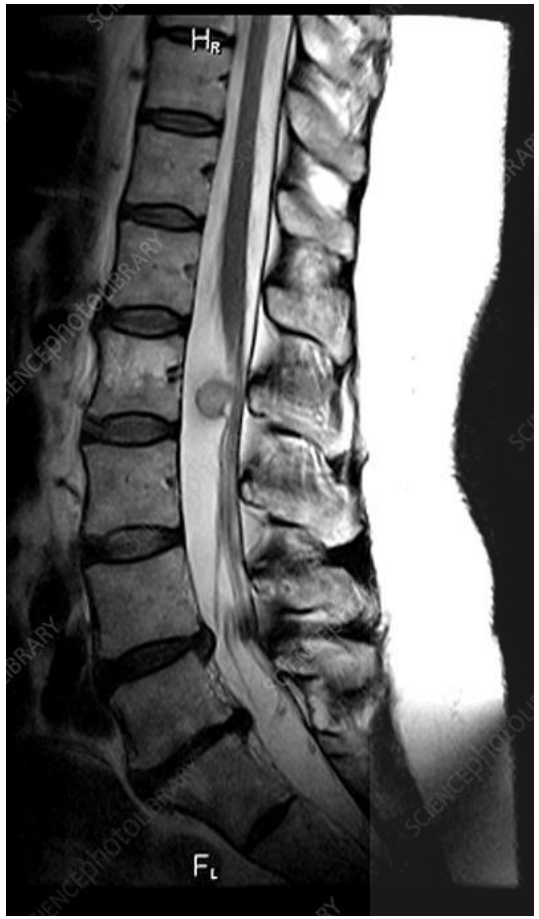


Nerve root lesions

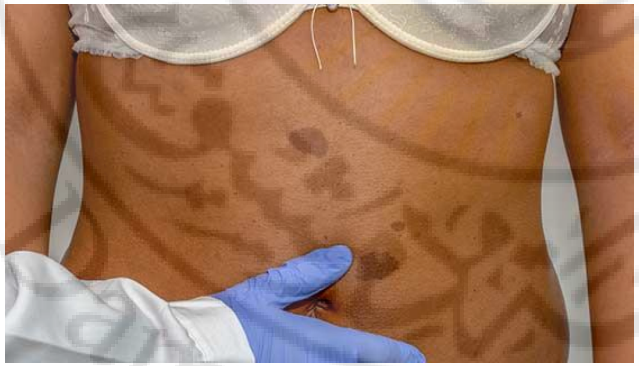


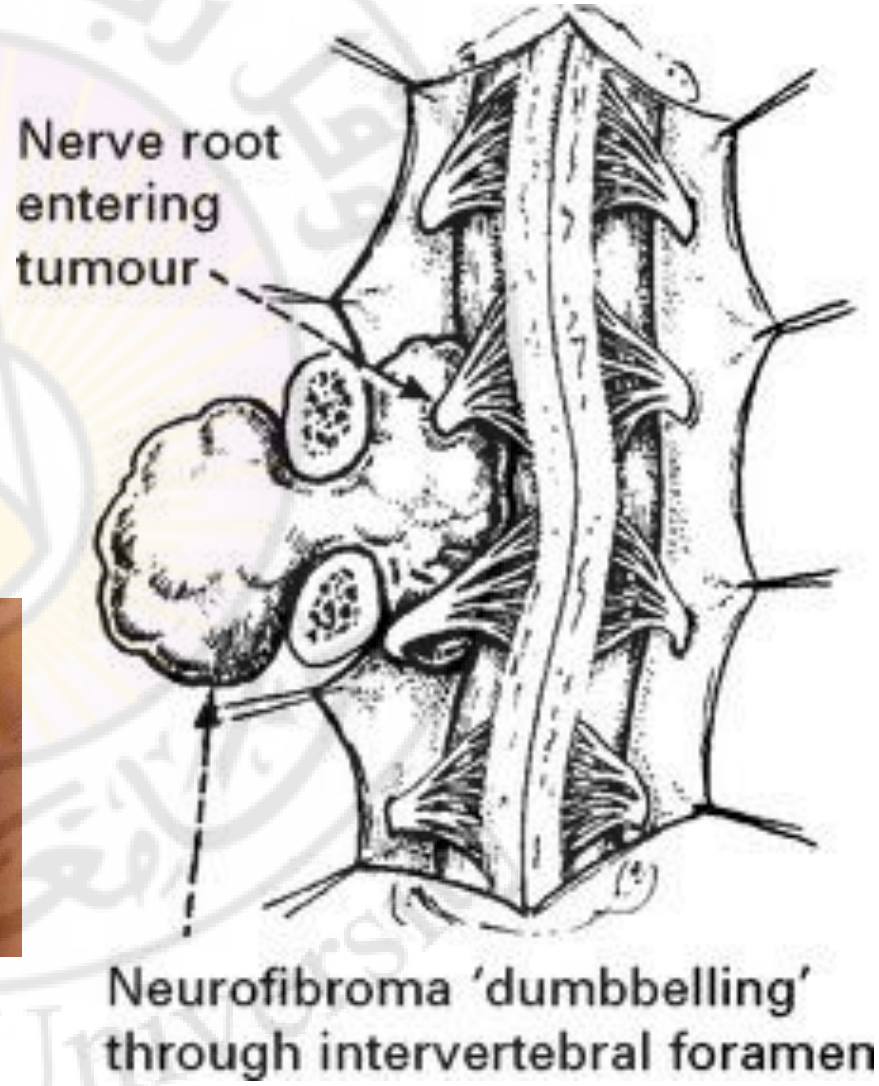
Girdle pain when affecting the trunk, i.e. between T3 and L2.

Nerve root lesions



Lumbar neurofibroma

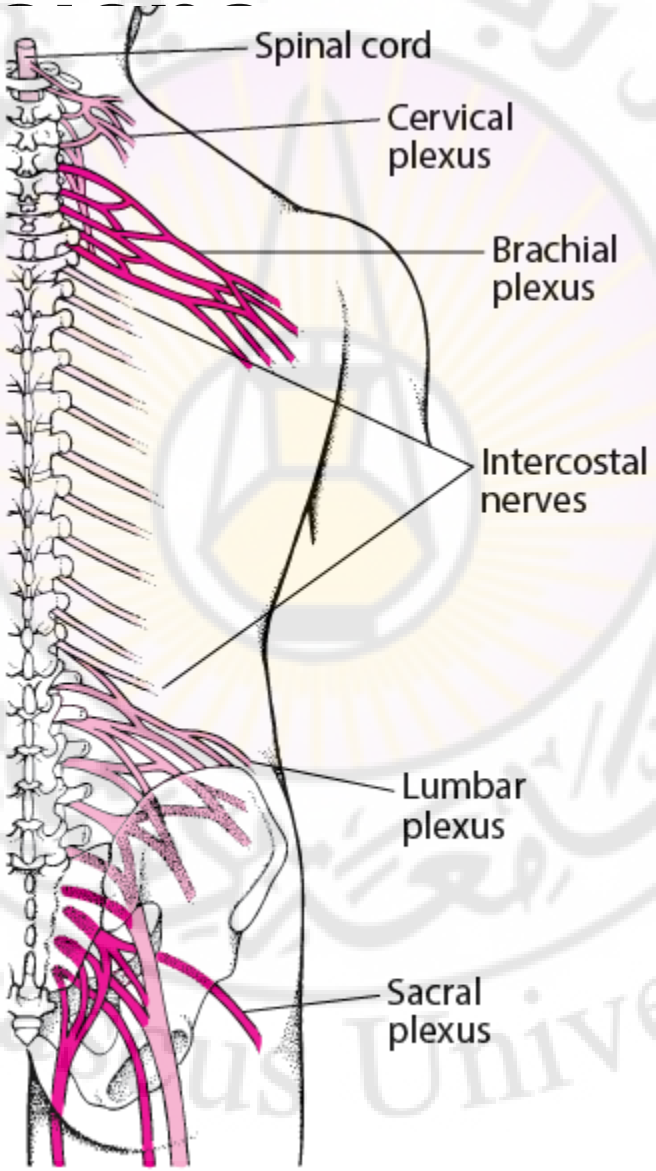




Nerve root lesions

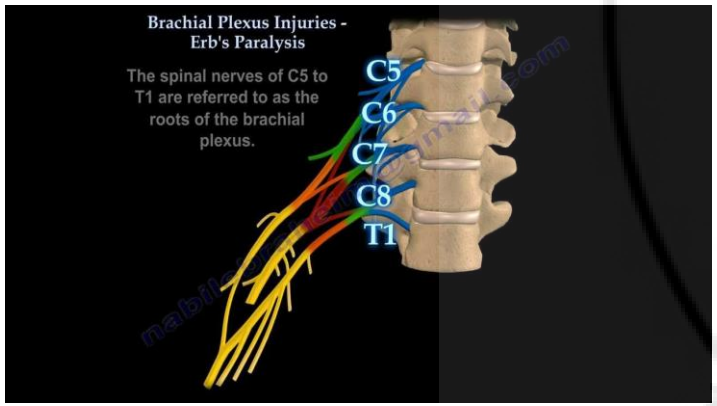
Lesions of the brachial plexus.

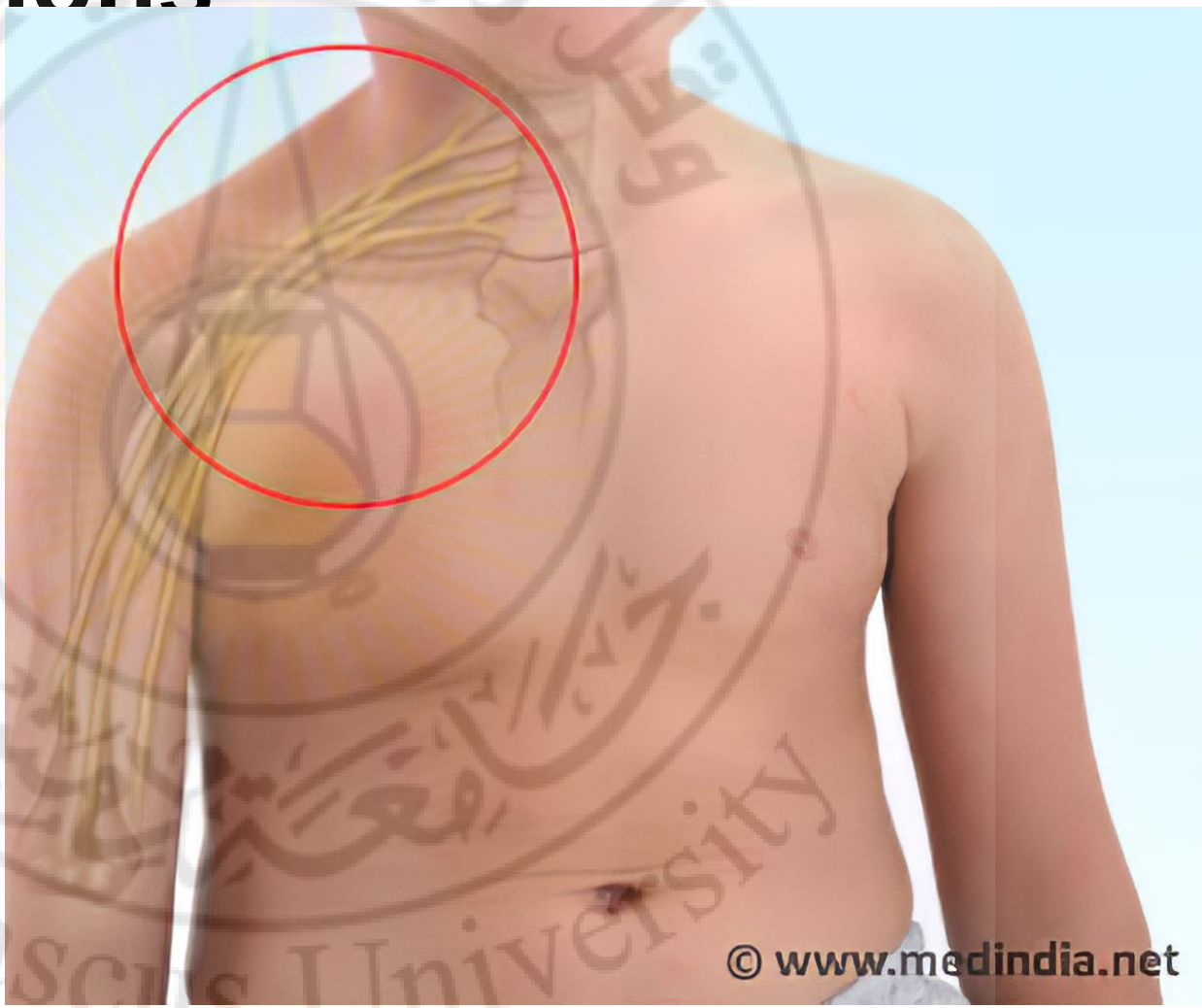
Lesions of the lumbosacral plexus.



Nerve root lesions

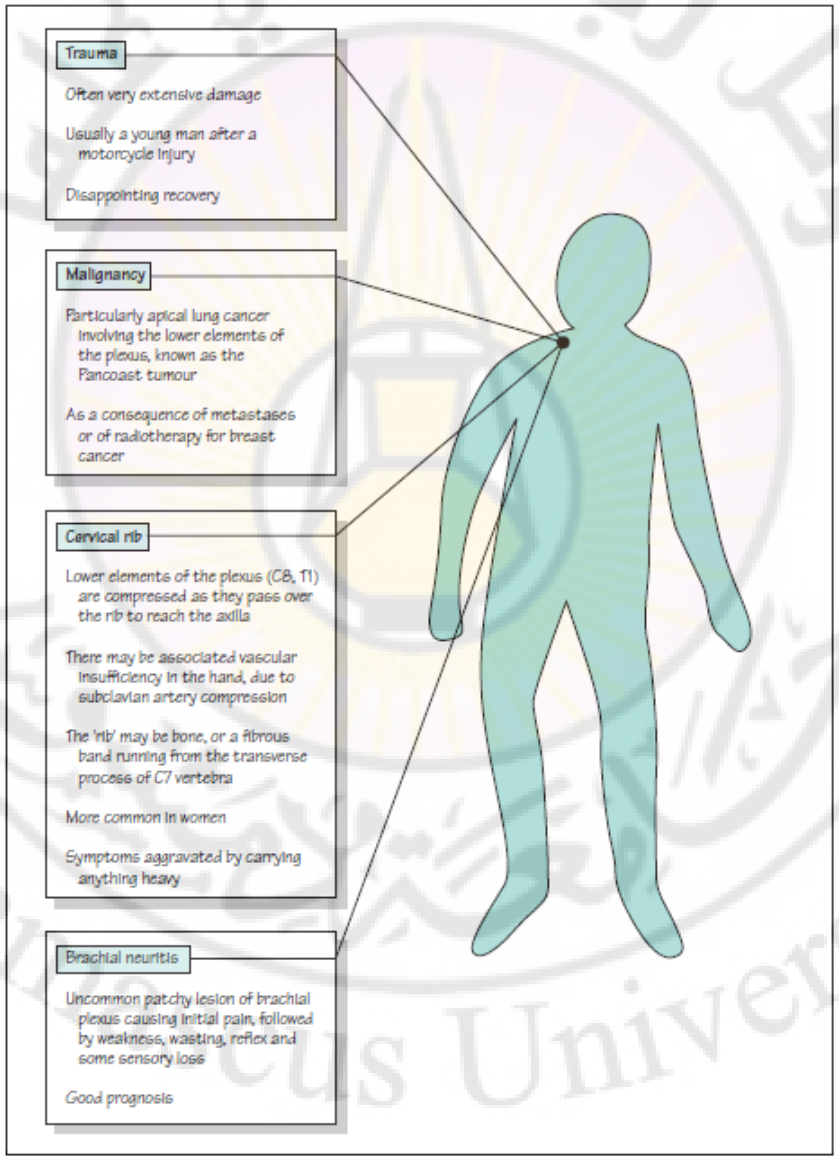
Lesions of the brachial plexus.





Nerve root

Lesions of the brachial plexus.



Nerve root lesions

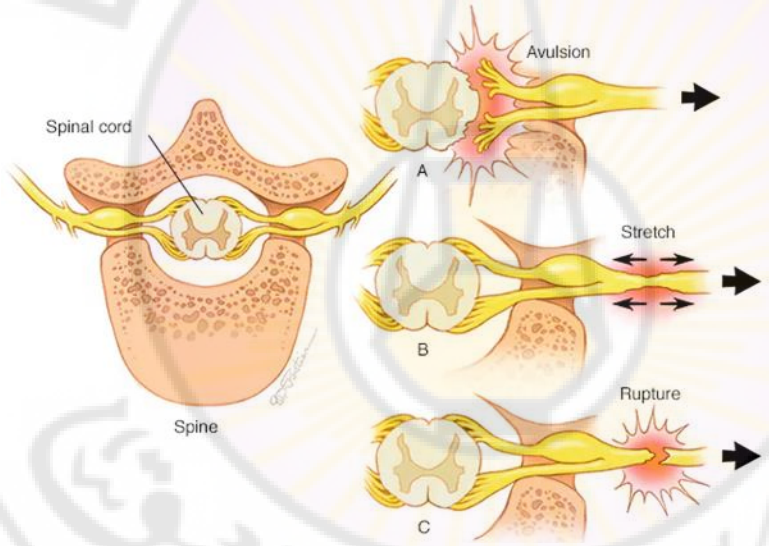
Lesions of the brachial plexus.

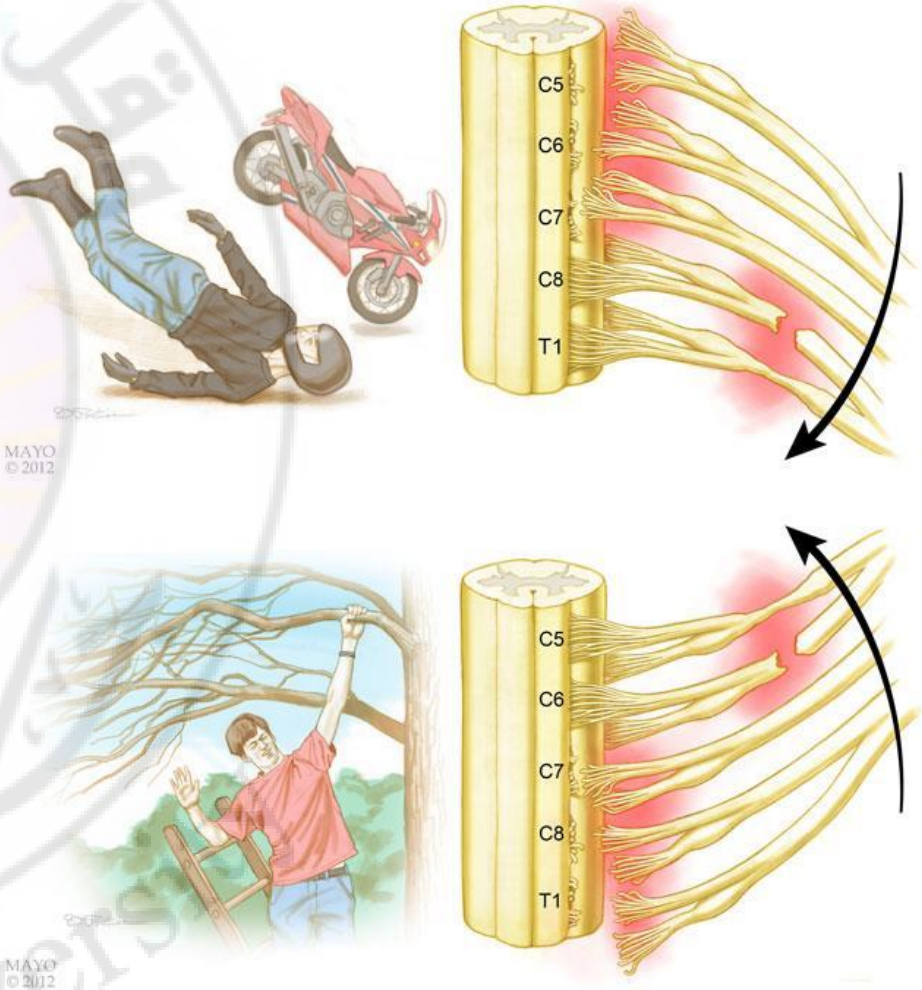
Trauma

Often very extensive damage

Usually a young man after a motorcycle injury

Disappointing recovery





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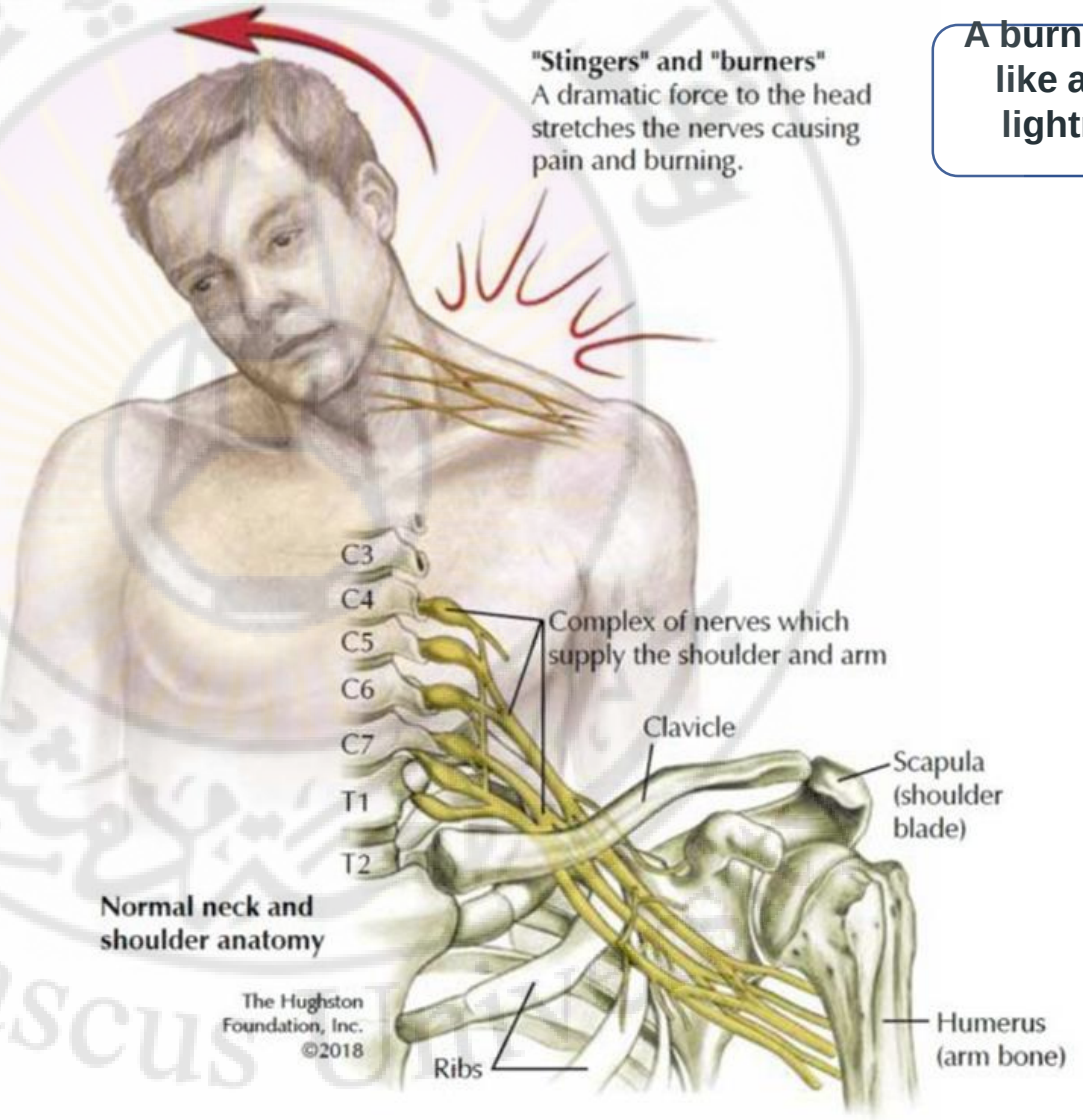
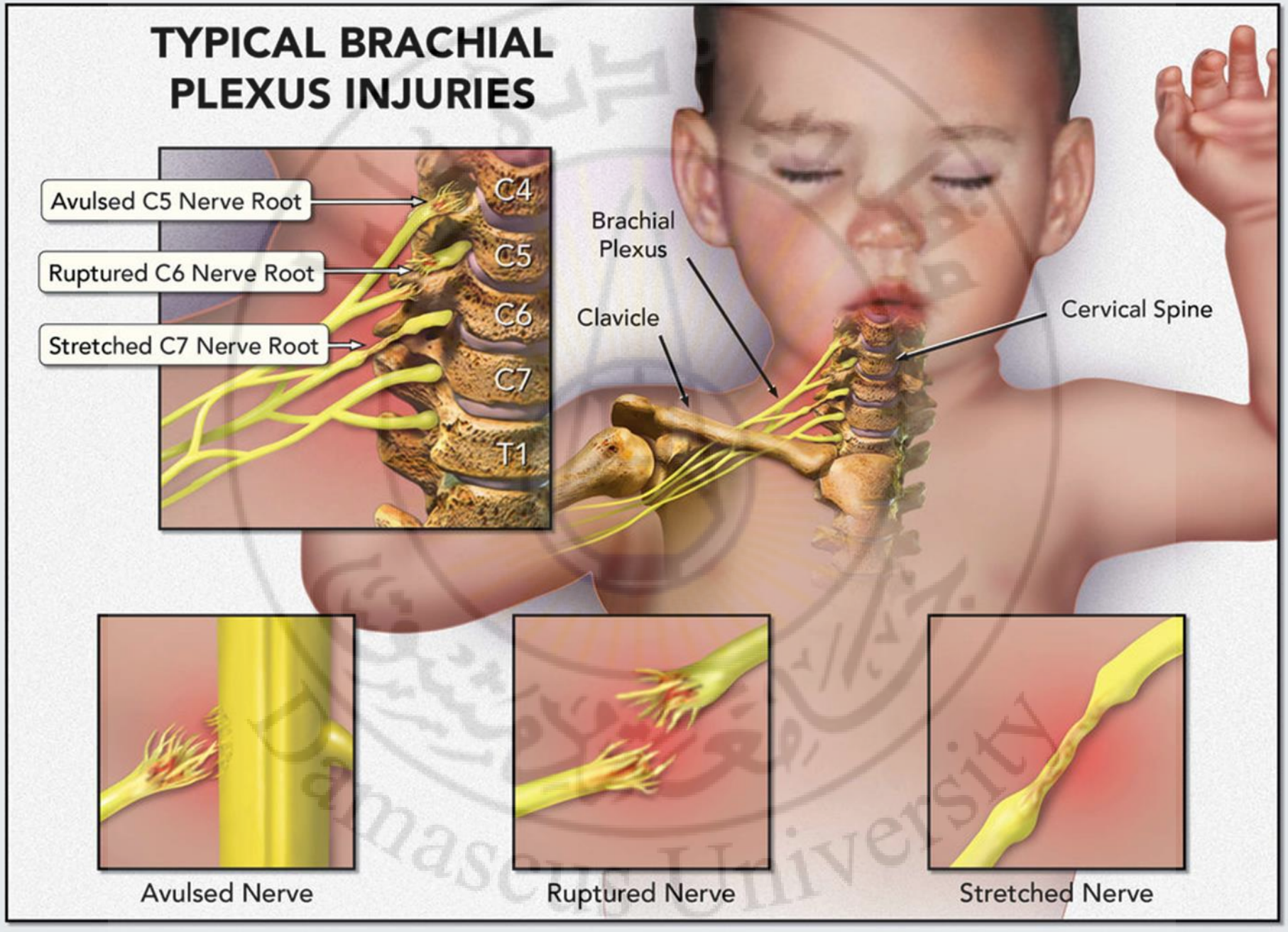
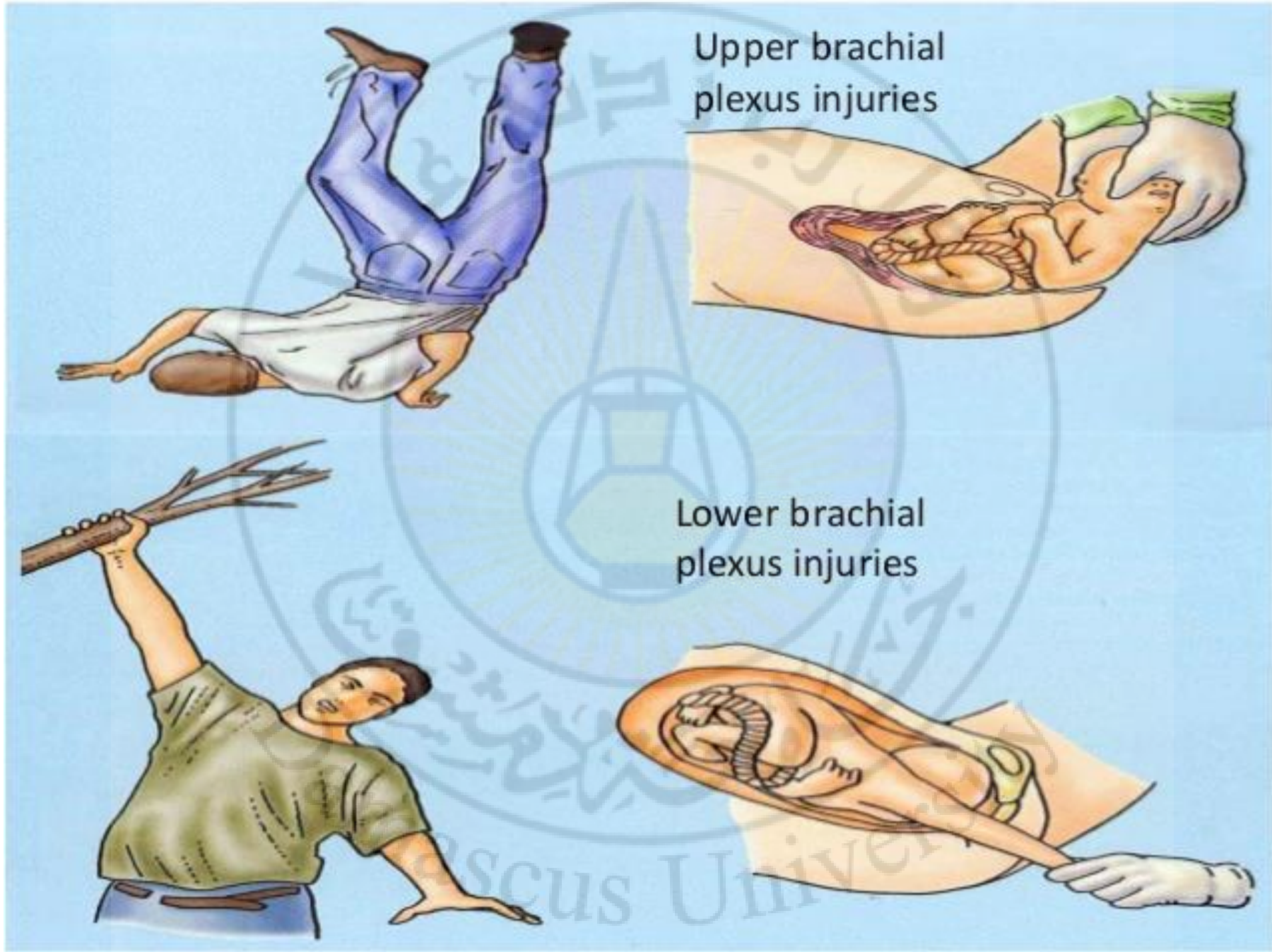


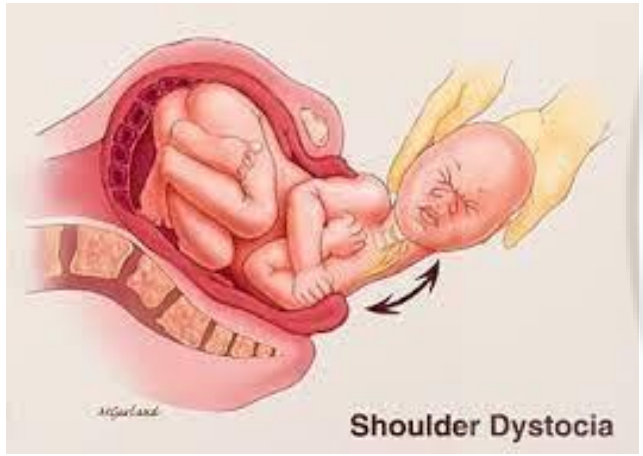
A burner or stinger can feel like an electric shock or lightning bolt down the arm.

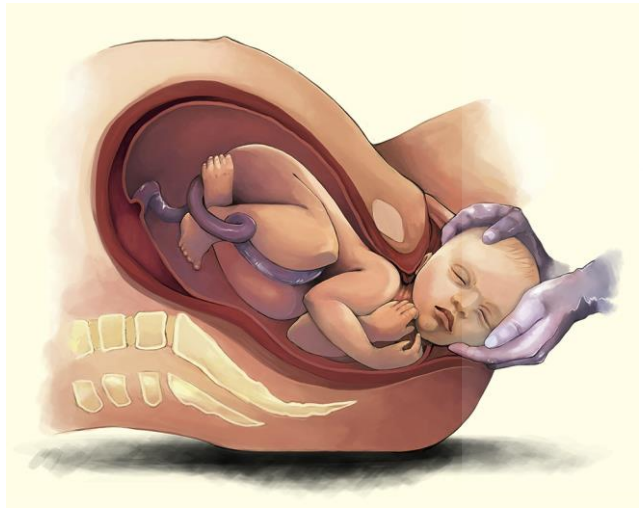

TYPICAL BRACHIAL PLEXUS INJURIES
Avulsed C5 Nerve Root
Ruptured C6 Nerve Root
Stretched C7 Nerve Root
C4
C5
C6
C7
T1
Brachial Plexus
Clavicle
Cervical Spine
Avulsed Nerve
Ruptured Nerve
Stretched Nerve

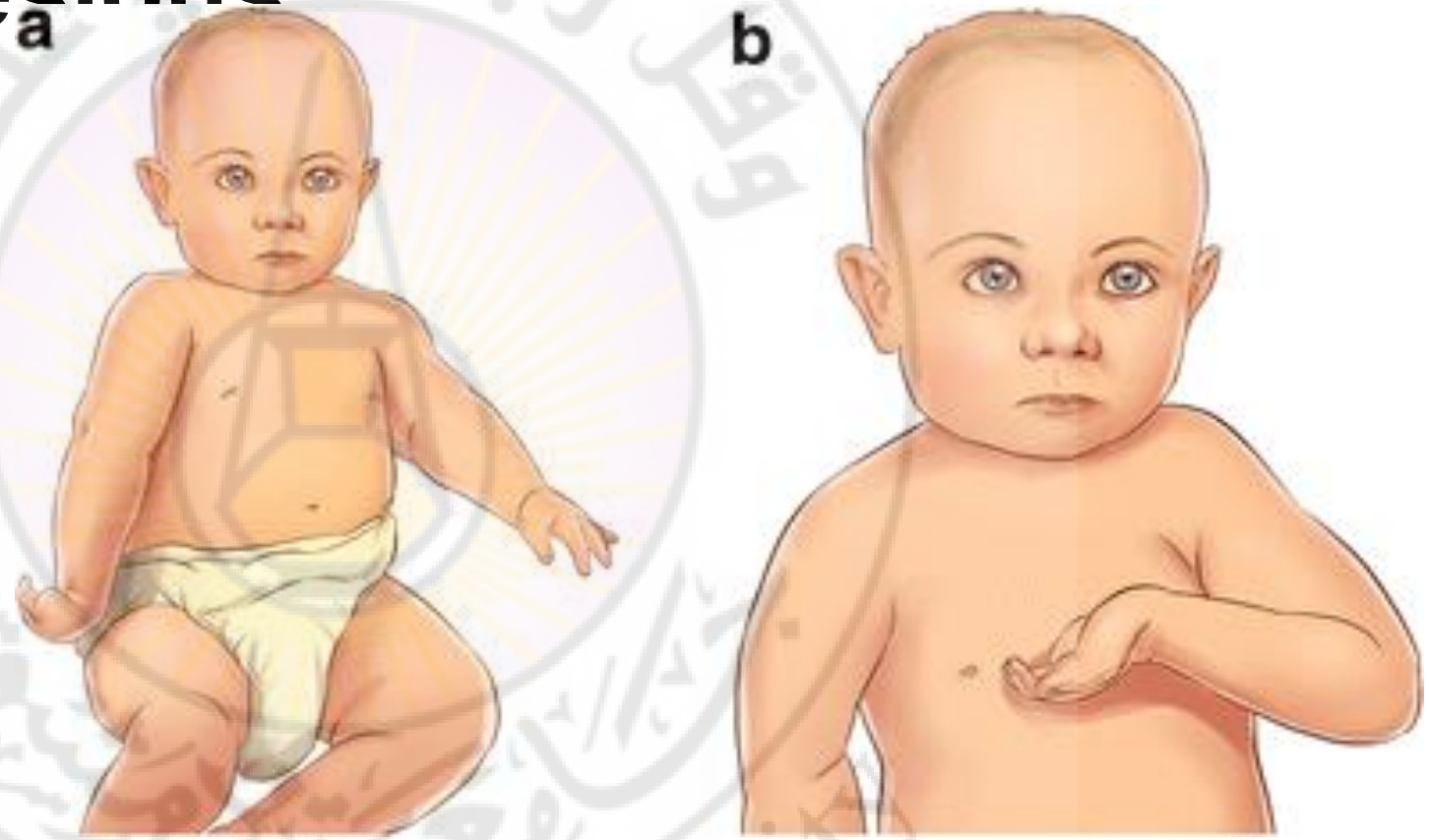

Upper brachial
plexus injuries
Lower brachial
plexus injuries

Nerve root lesions

Lesions of the brachial plexus.







a Duchenne-Erb (upper trunk) palsy. Shoulder abduction and elbow flexion are paralyzed.

b Dejerine-Klumke (lower trunk) palsy. The shoulder and elbow are preserved, but the hand is paralyzed

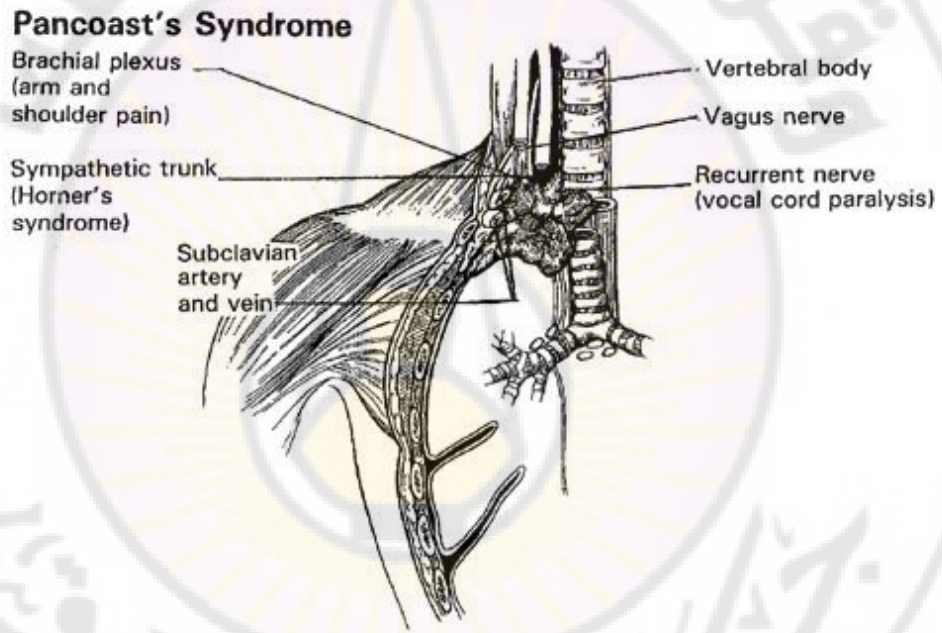
Nerve root lesions

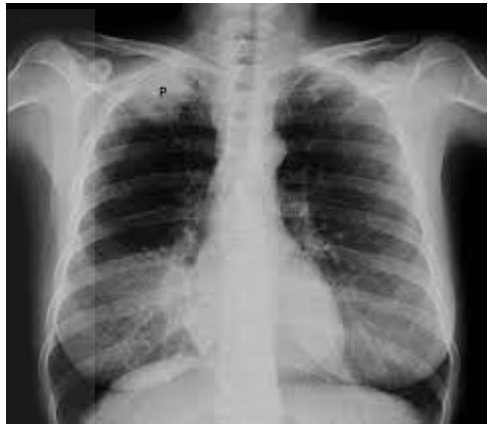
Lesions of the brachial plexus.

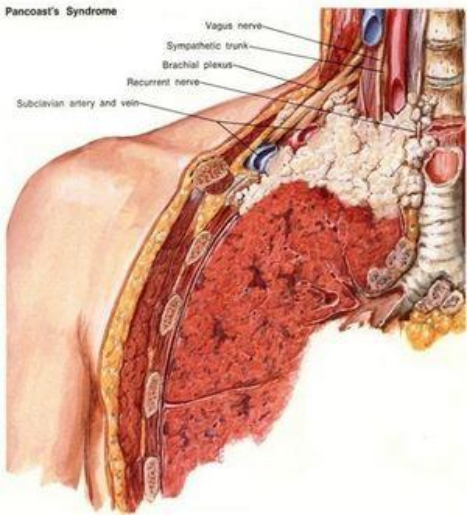
Malignancy

Particularly apical lung cancer involving the lower elements of the plexus, known as the Pancoast tumour

As a consequence of metastases or of radiotherapy for breast cancer







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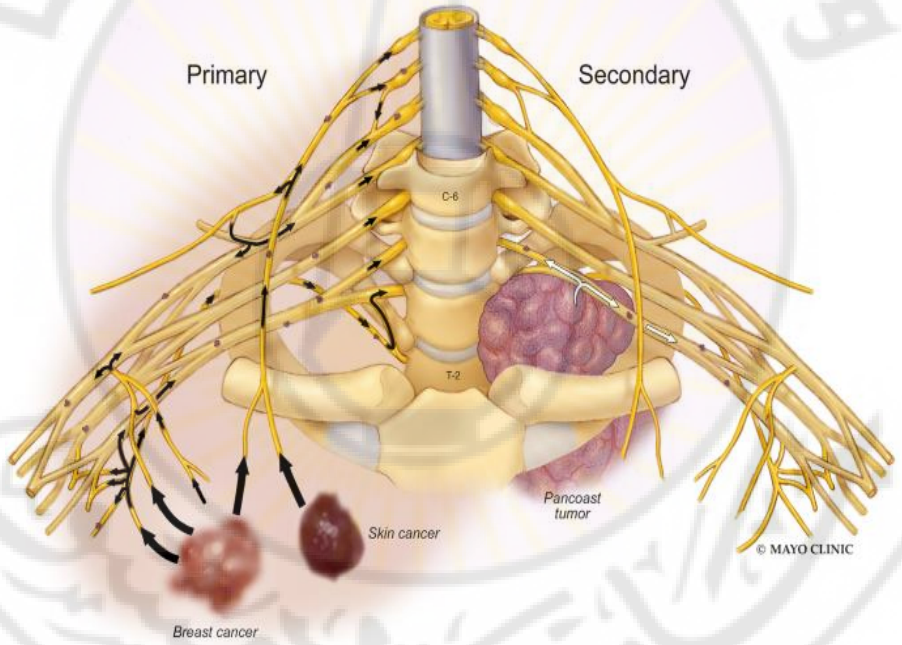
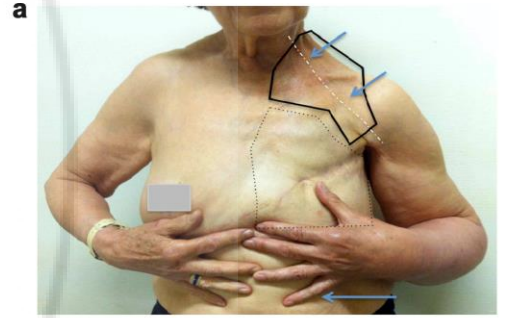
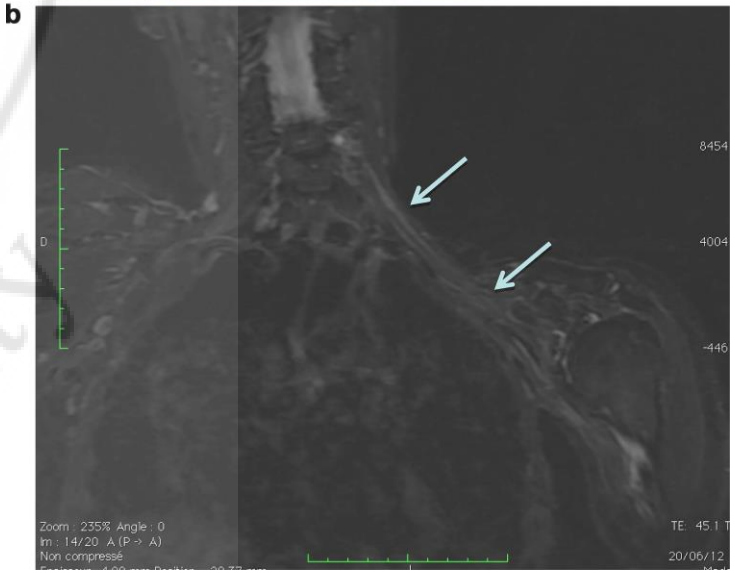
Particularly apical lung cancer involving the lower elements of the plexus, known as the Pancoast tumour

As a consequence of metastases or of radiotherapy for breast cancer







Nerve root lesions

Lesions of the brachial plexus.

Cervical rib

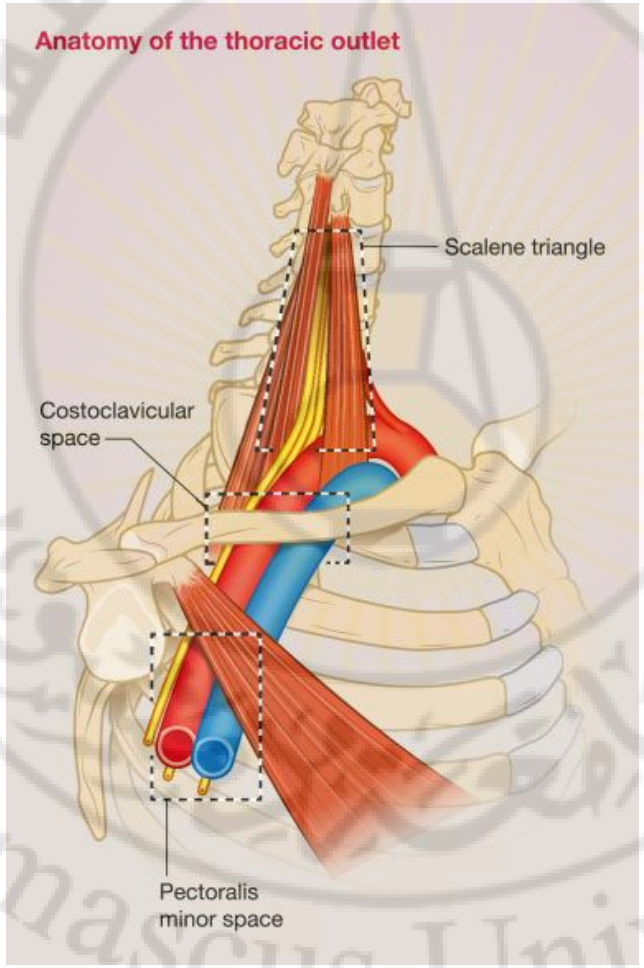
Lower elements of the plexus (C8, T1) are compressed as they pass over the rib to reach the axilla

There may be associated vascular insufficiency in the hand, due to subclavian artery compression

The 'rib' may be bone, or a fibrous band running from the transverse process of C7 vertebra

More common in women

Symptoms aggravated by carrying anything heavy



Thoracic outlet syndrome (TOS) is a condition in which there is compression of the nerves, arteries, or veins in the passageway from the lower neck to the armpit.[1] There are three main types: neurogenic, venous, and arterial.[1] The neurogenic type is the most common and presents with pain, weakness, paraesthesia, and occasionally loss of muscle at the base of the thumb.[1][2] The venous type results in swelling, pain, and possibly a bluish coloration of the arm.[2] The arterial type results in pain, coldness, and pallor of the arm.

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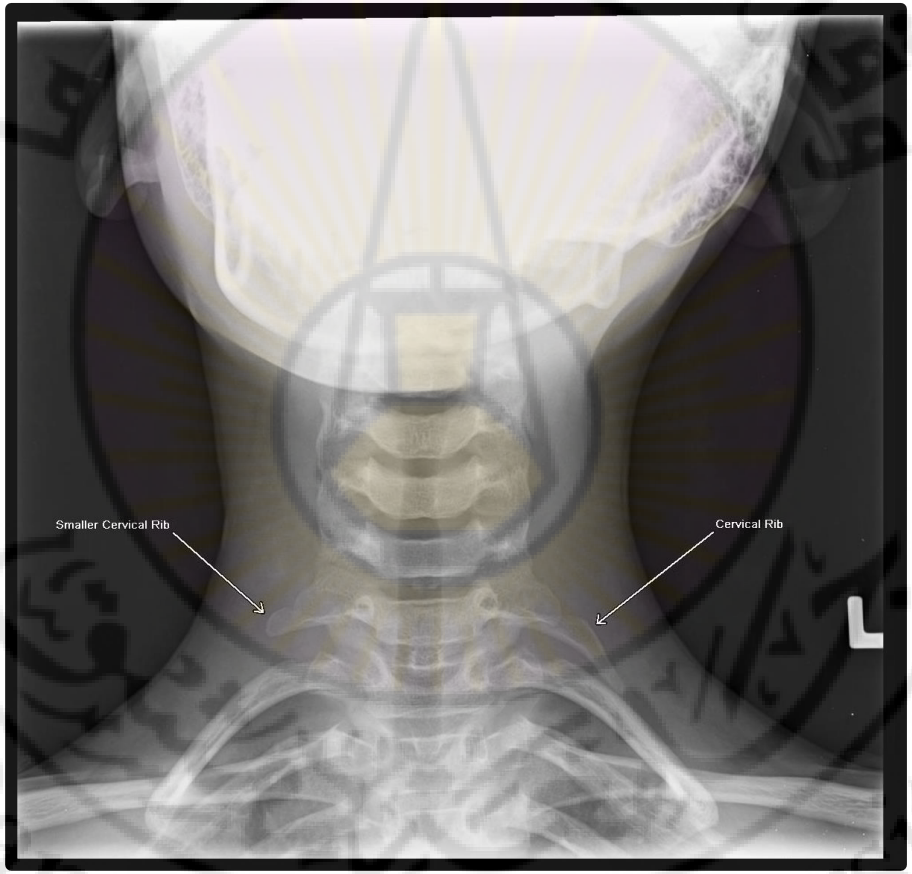
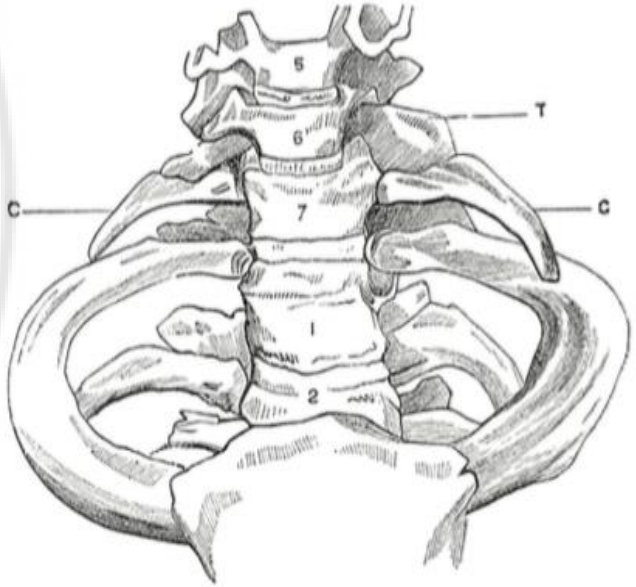


Chest X-ray demonstrating bilateral cervical ribs (indicated by the arrows)



A cervical rib in humans is an extra rib which arises from the seventh cervical vertebra

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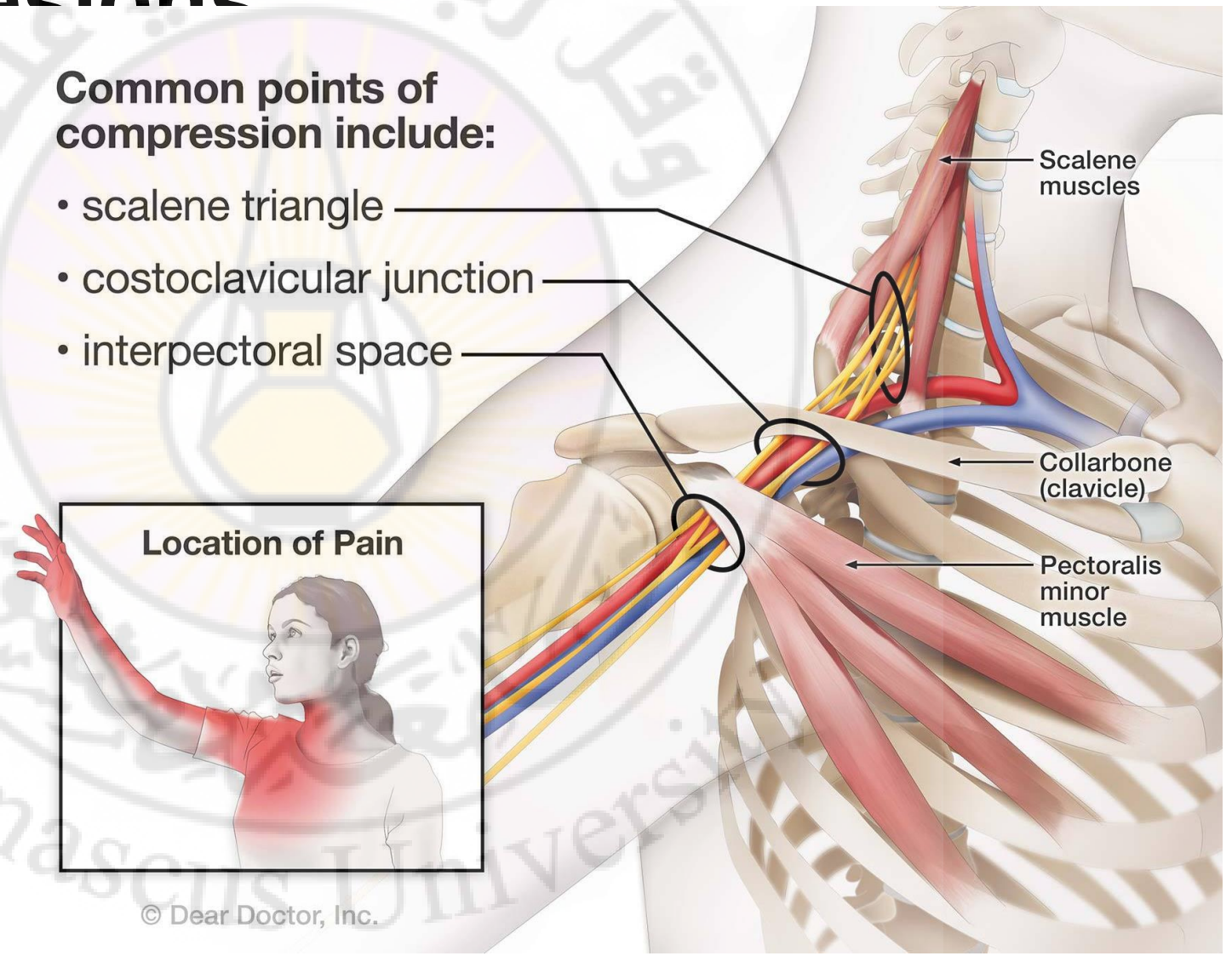

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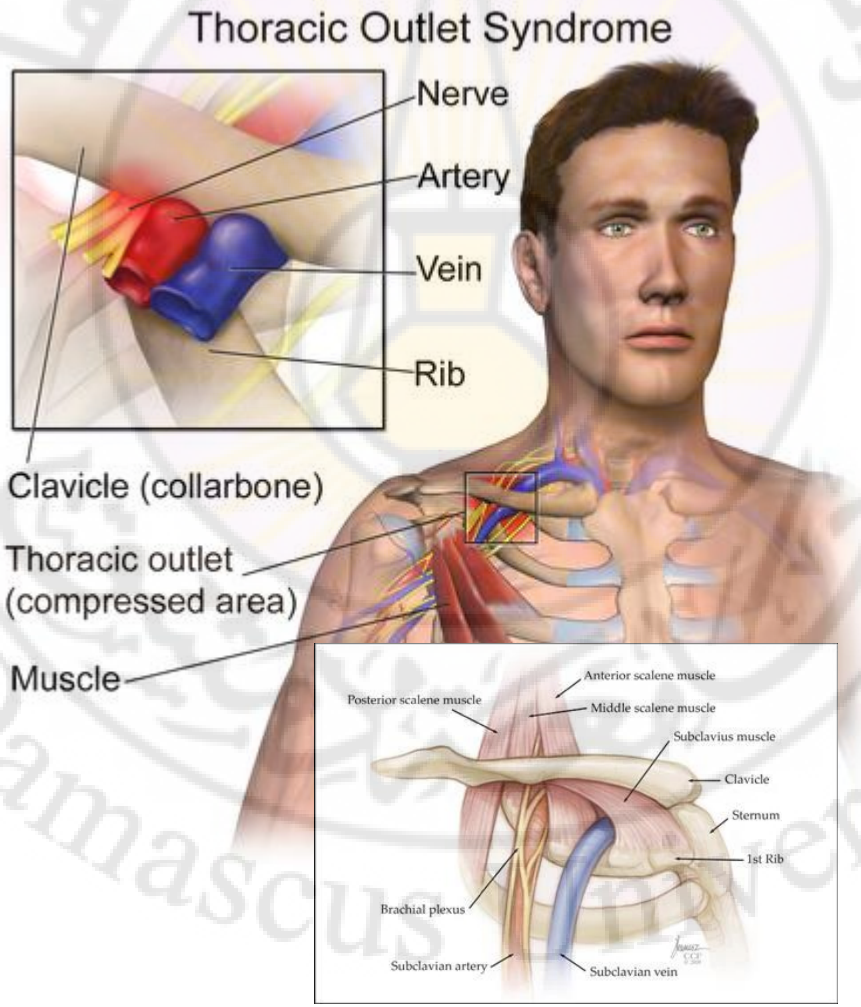


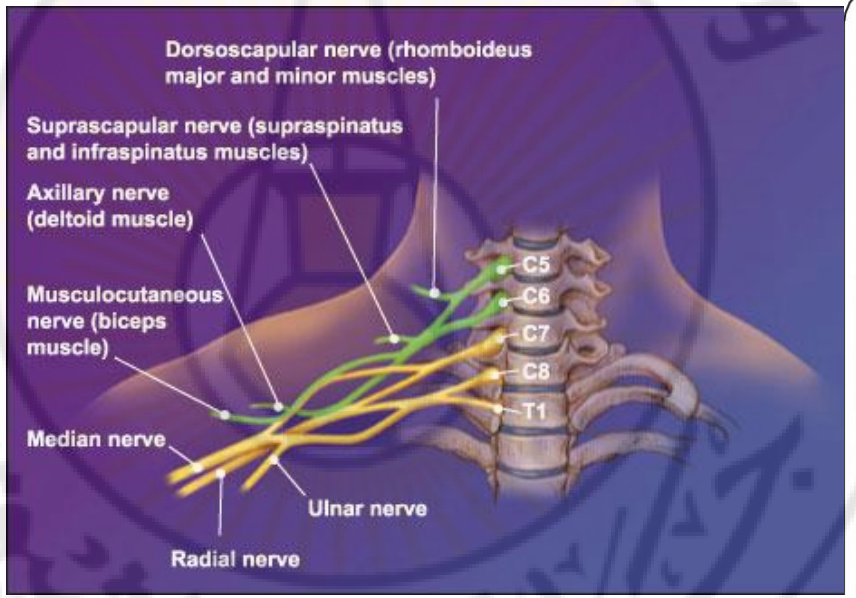
Nerve root lesions

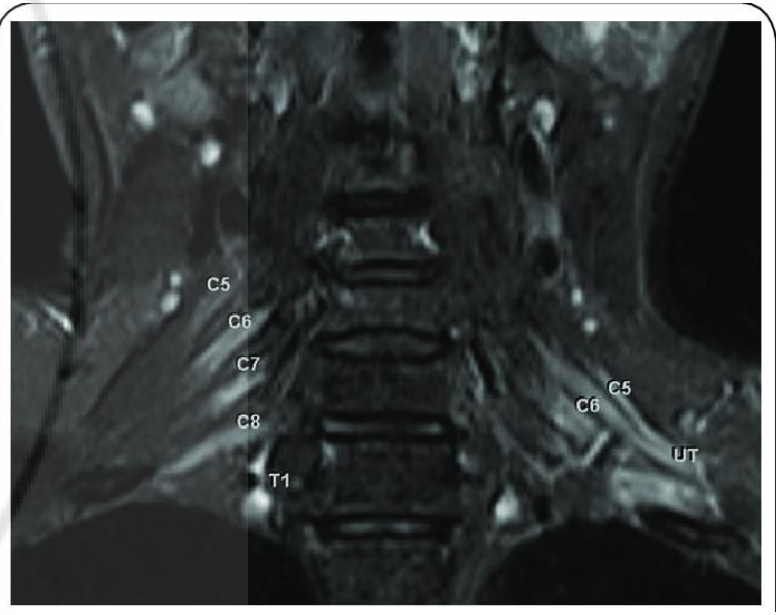
Lesions of the brachial plexus.

Brachial neuritis

Uncommon patchy lesion of brachial plexus causing initial pain, followed by weakness, wasting, reflex and some sensory loss

Good prognosis





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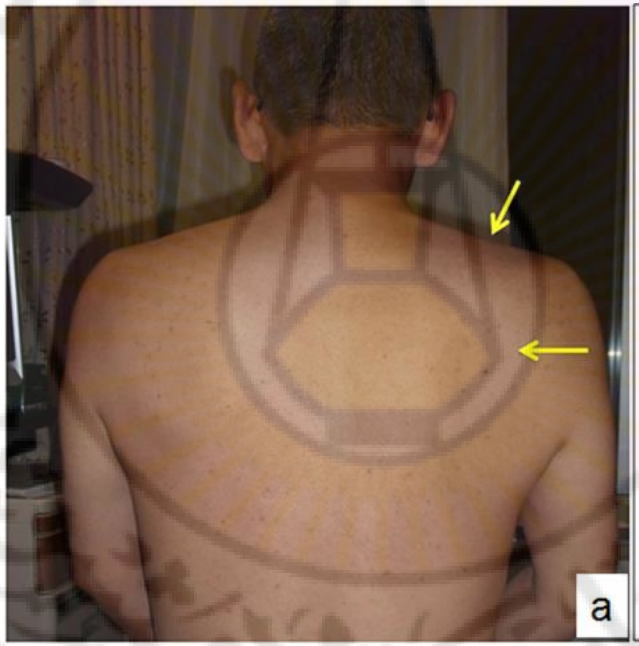


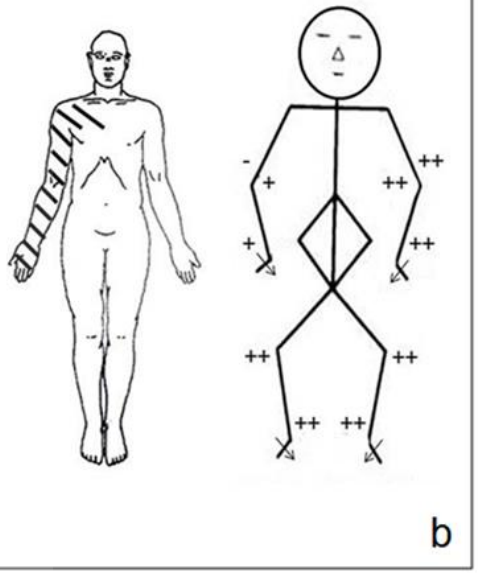
Twelve cranial nerves: normal

MMT (right/left):

Deltoid (C5)	5/5
Biceps (C5, 6)	5/5
Triceps (C6-8)	5/5
Wrist flexion (C6)	4/5
Finger extensors (C7)	3/5
Finger openers (C8, Th1)	3/5
Lower-extremity muscles	5/5

Sensational systems:

- Hypesthesia and hypalgesia in his right C5-Th2 area (solid lines)
- Weakness of vibration in his right scapula



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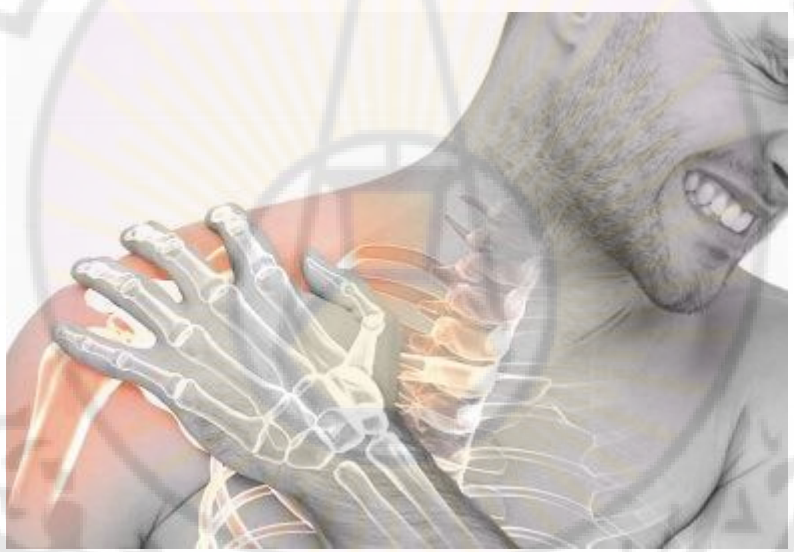
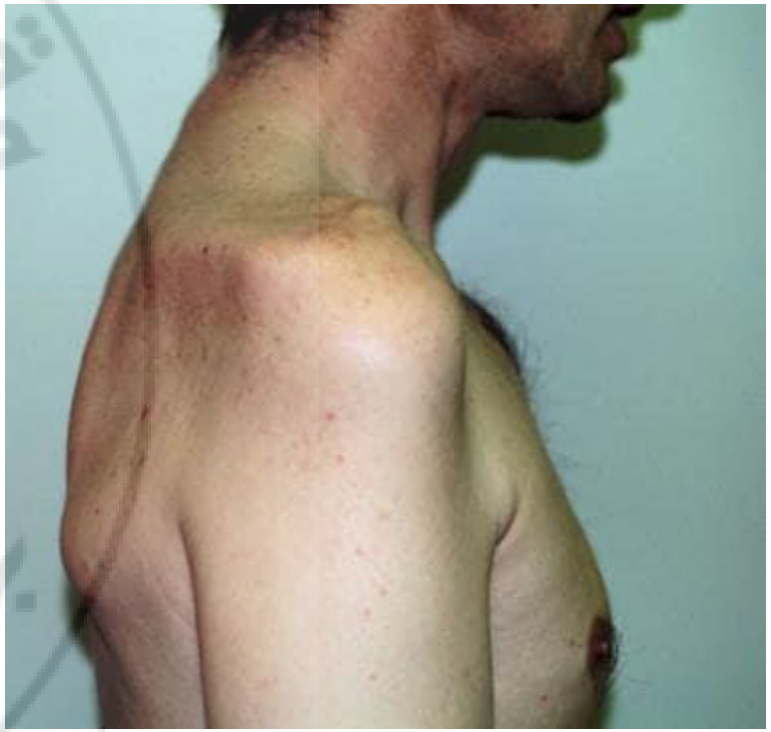
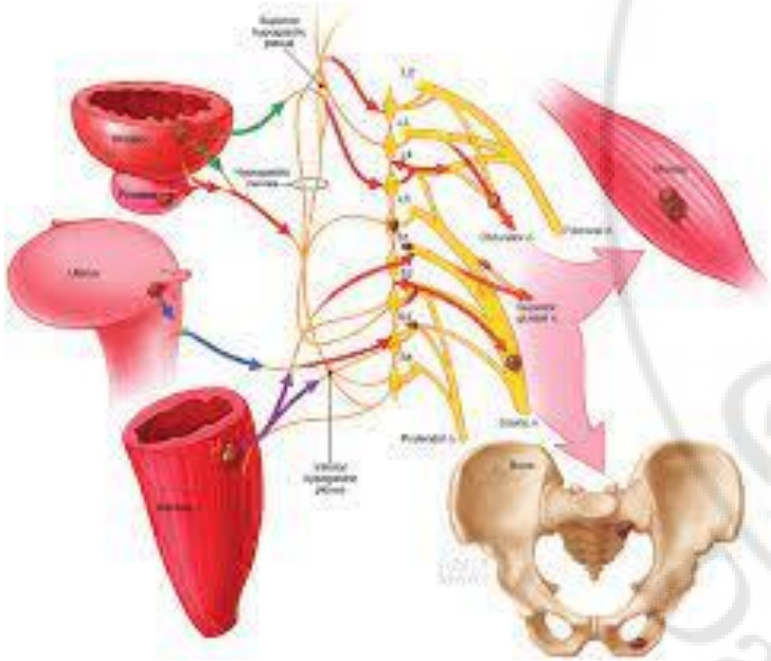
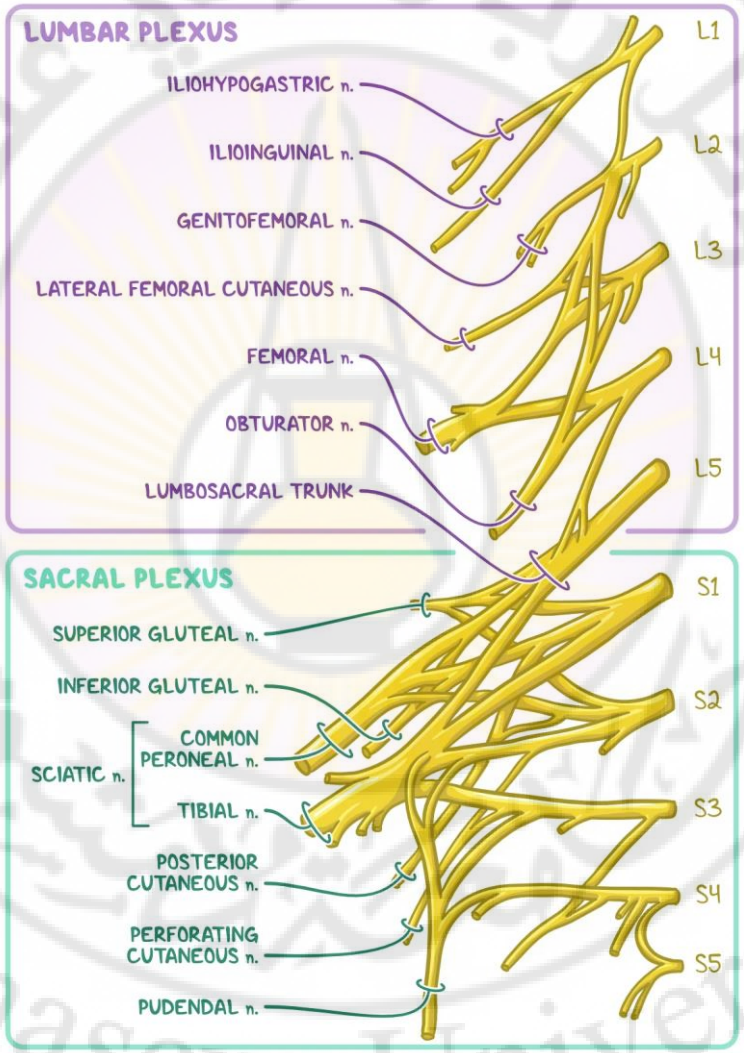




Nerve root lesi

Lesions of the lumbosacral plexus.

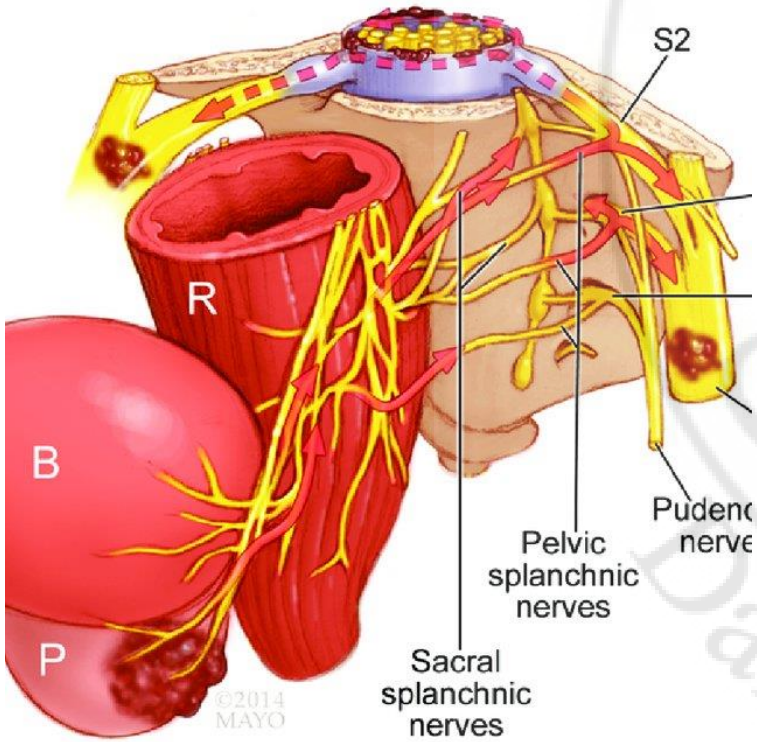


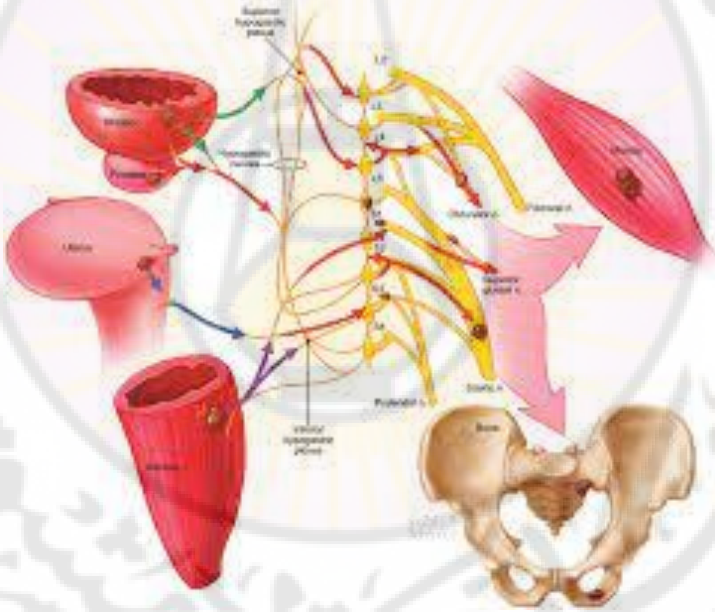


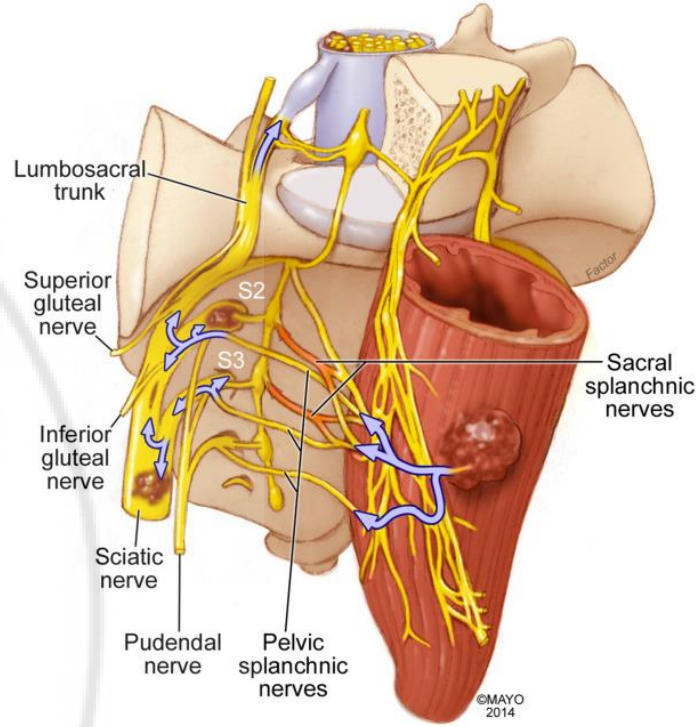
Spinal nerves from L2 to S2

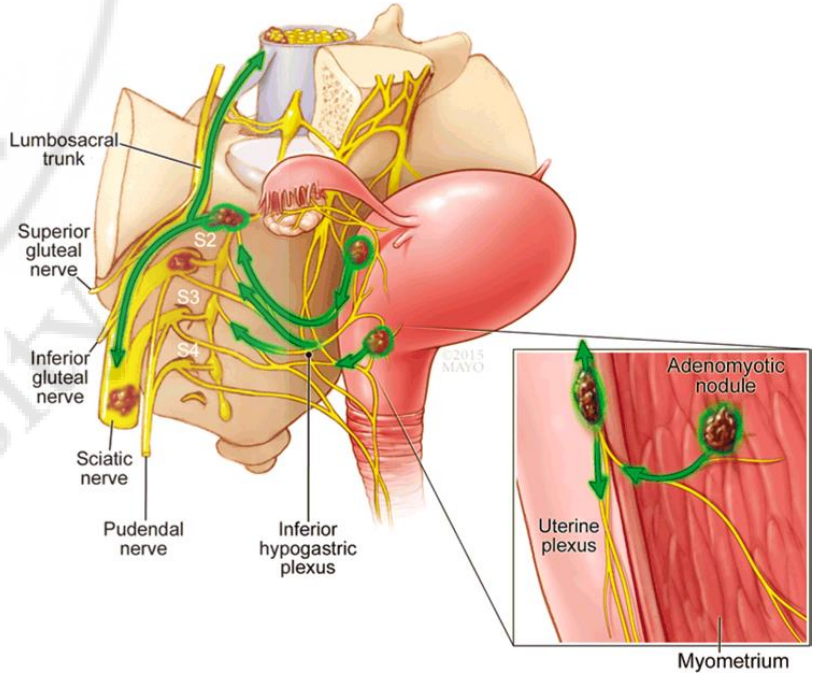
Nerve root lesions

Lesions of the lumbosacral plexus.



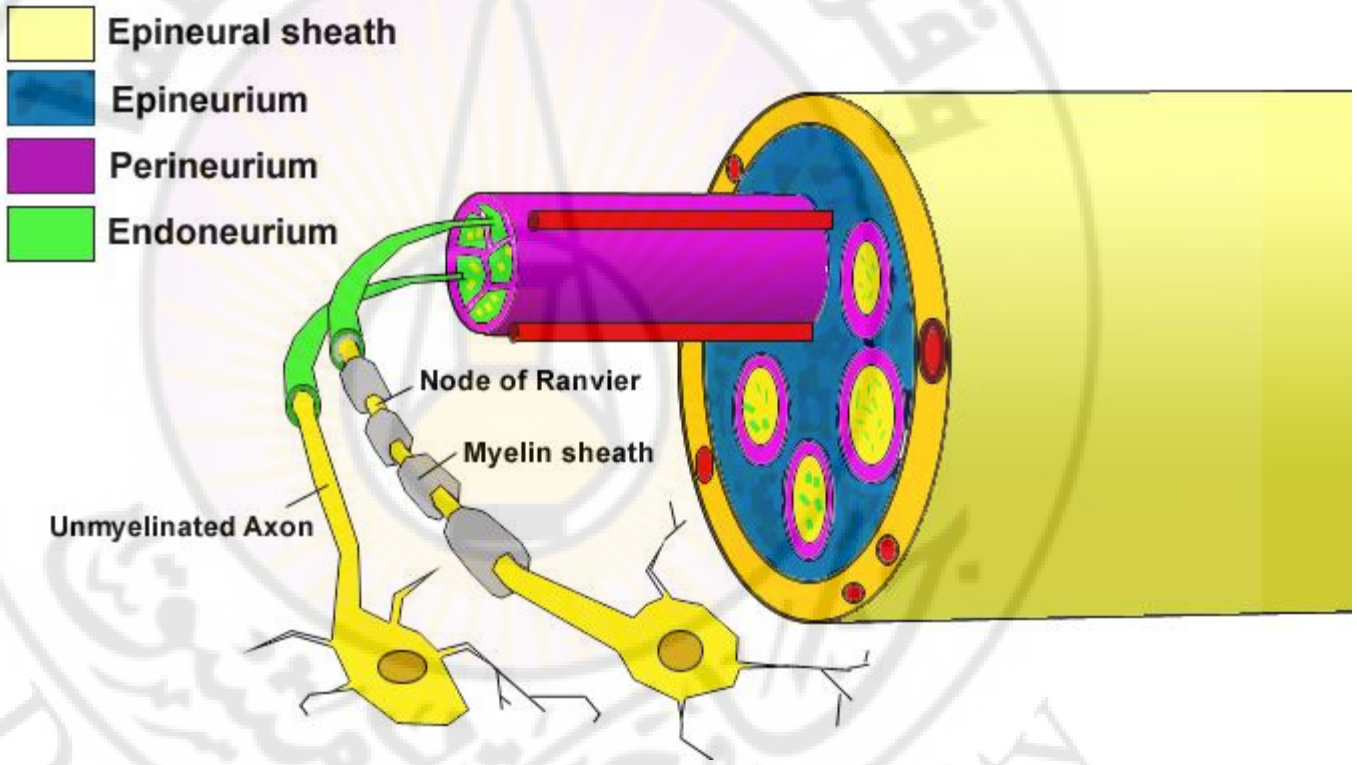






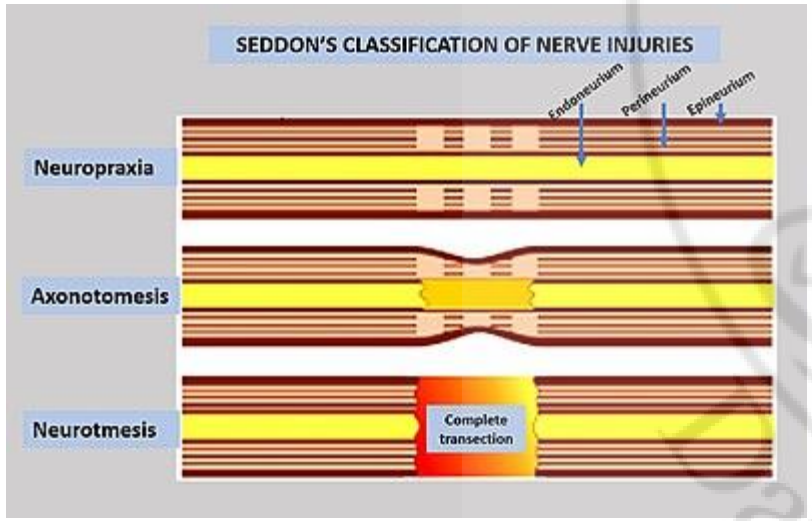
Spinal nerves from L2 to S2

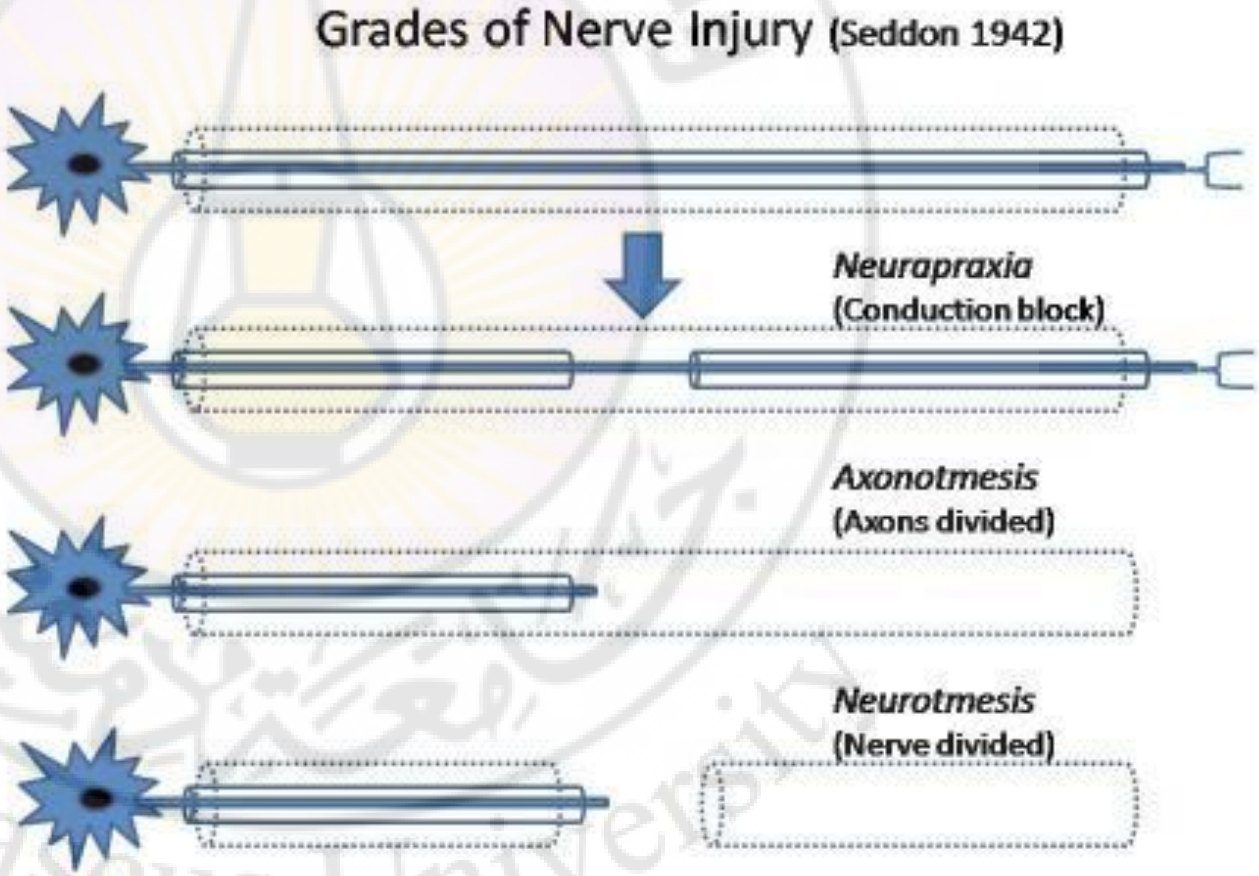
Peripheral nerve lesions



Individual peripheral nerves in the limbs may be damaged by any of five mechanisms

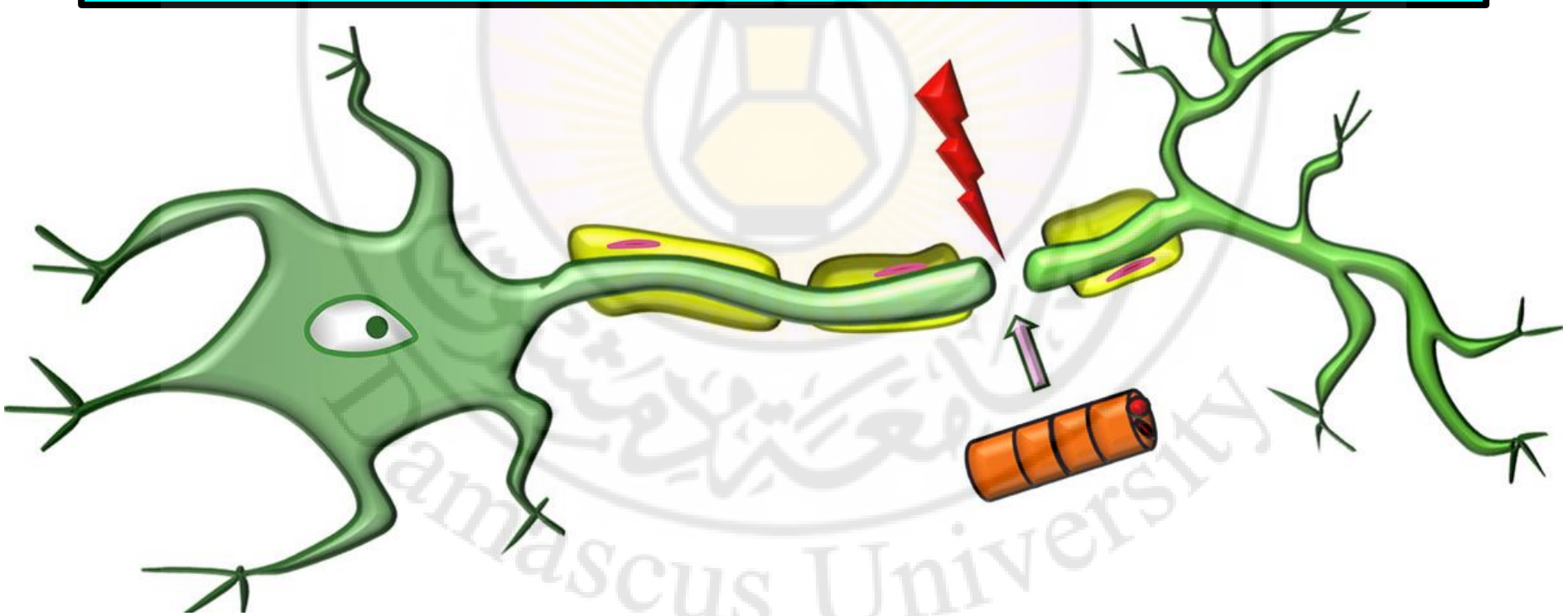
Peripheral nerve lesions



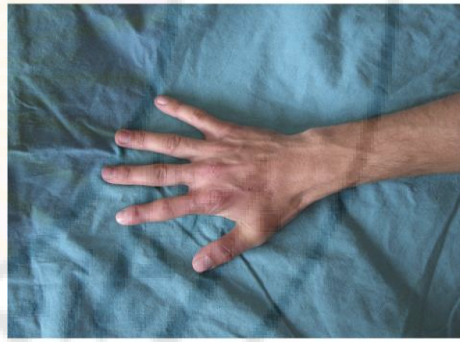


Peripheral nerve lesions

1. Trauma: in wounds created by sharp objects such as knives or glass (e.g. median or ulnar nerve at the wrist), by inaccurate localization of intramuscular injections (e.g. sciatic nerve in the buttock), or by the trauma of bone fractures (e.g. radial nerve in association with a midshaft fracture of the humerus).

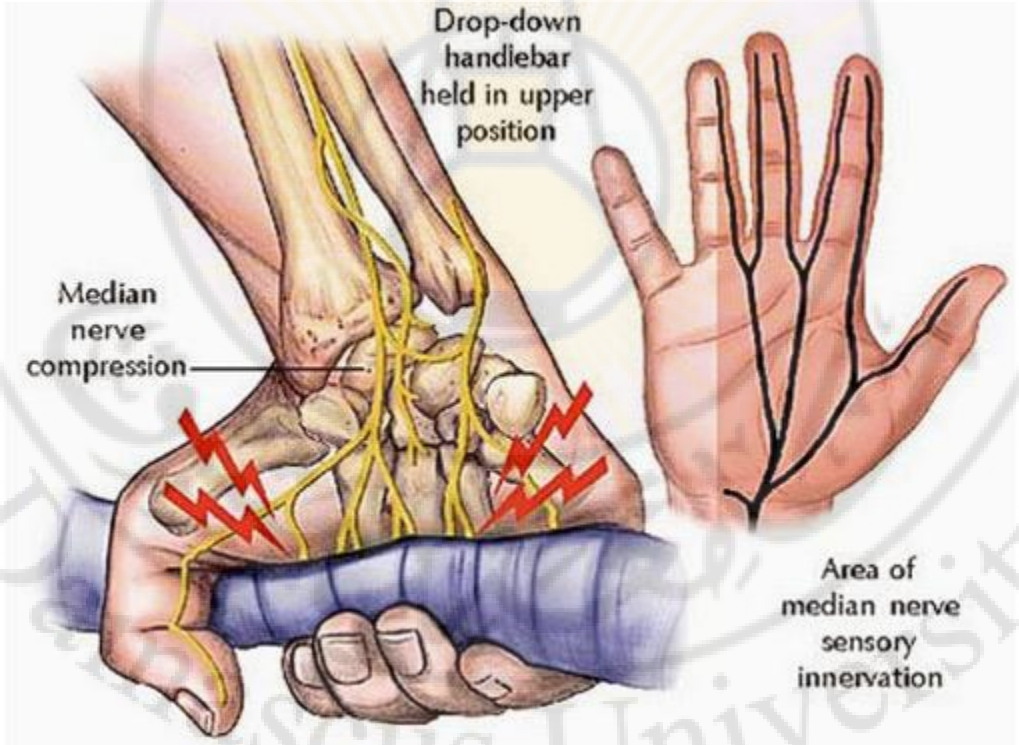


Peripheral nerve lesions



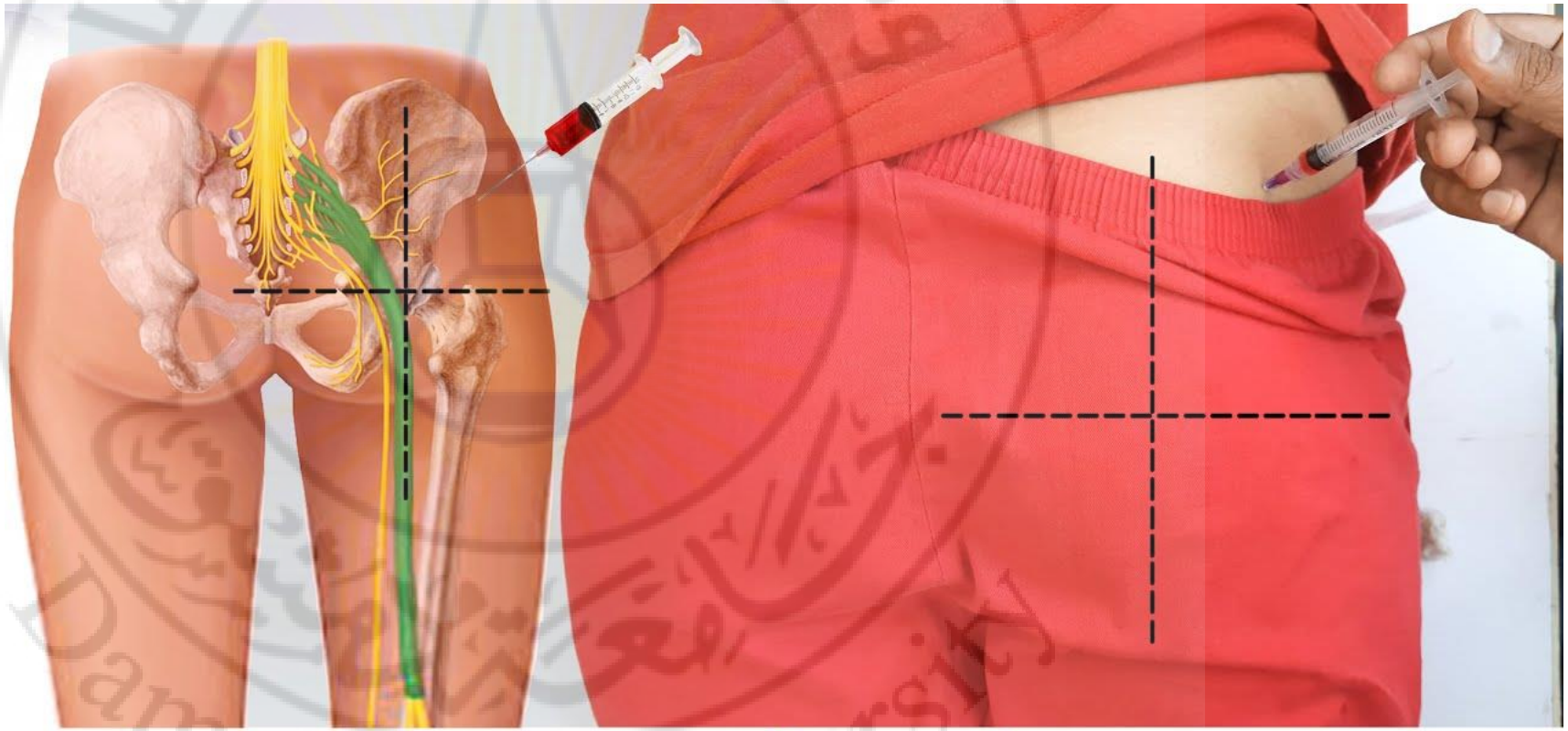
22-year-old male with glass-related injury (Case 2). The ulnar artery; ulnar nerve; FDS and FDP tendons of the fifth finger; and FCU tendon were cut. Later in his postoperative period, he had no signs of nerve injury or tendon adhesion.

Peripheral nerve lesions



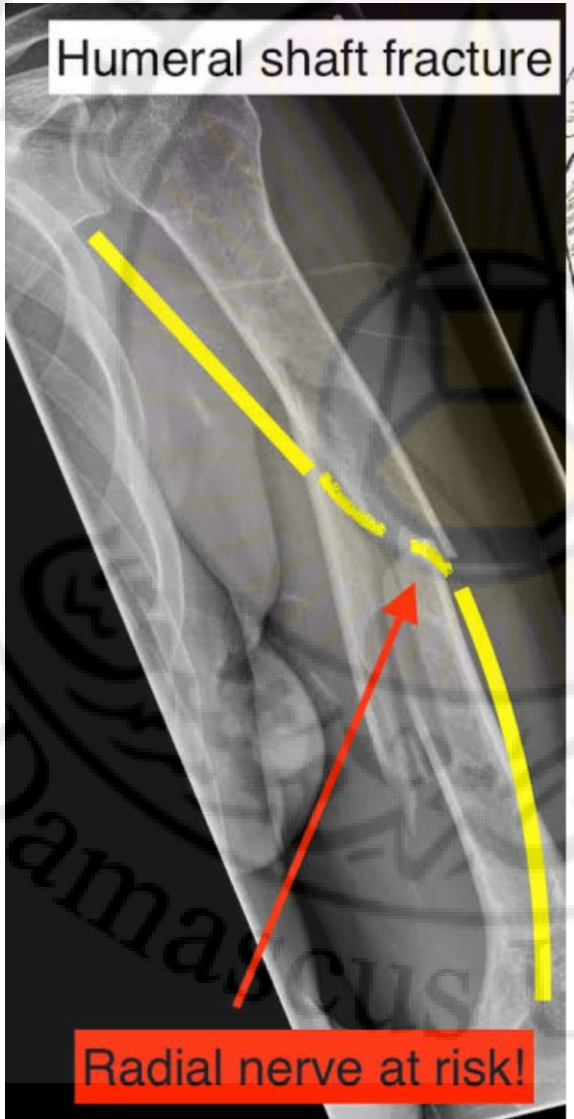
Nerve root lesions

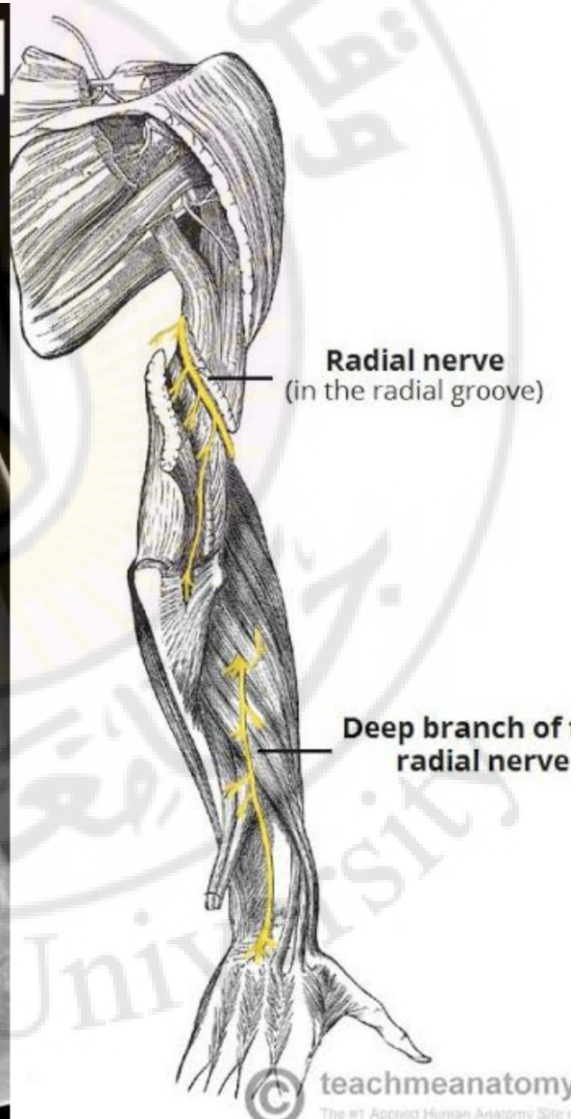
Peripheral nerve lesions



Peripheral nerve lesions

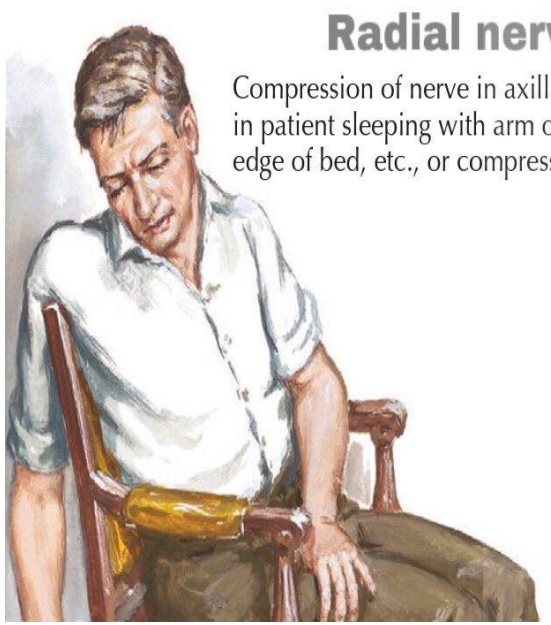
Radial nerve in association with a midshaft fracture of the humerus

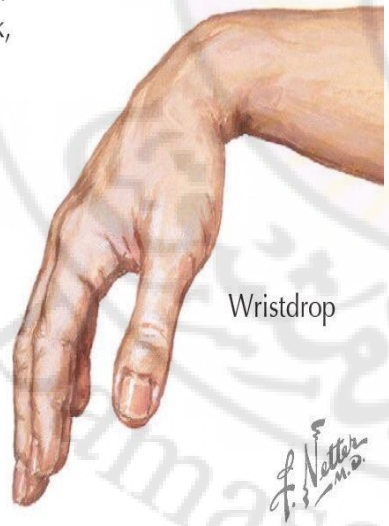


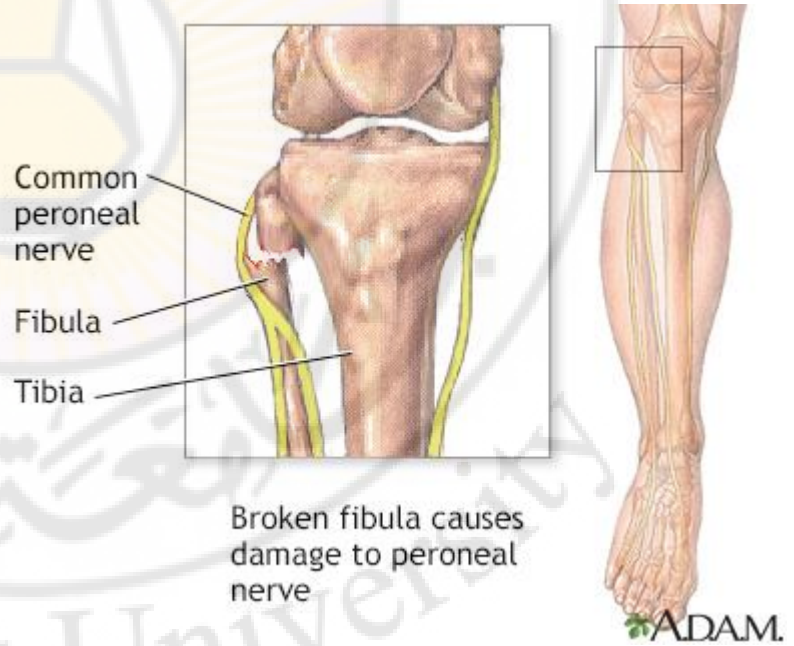


Peripheral nerve lesions

2. *Acute compression*: in which pressure from a hard object is exerted on a nerve. This may occur during sleep, anaesthesia or coma in which there is no change in the position of the body to relieve the compression (e.g. radial nerve compression against the posterior aspect of the humerus, common peroneal nerve against the lateral aspect of the neck of the fibula).

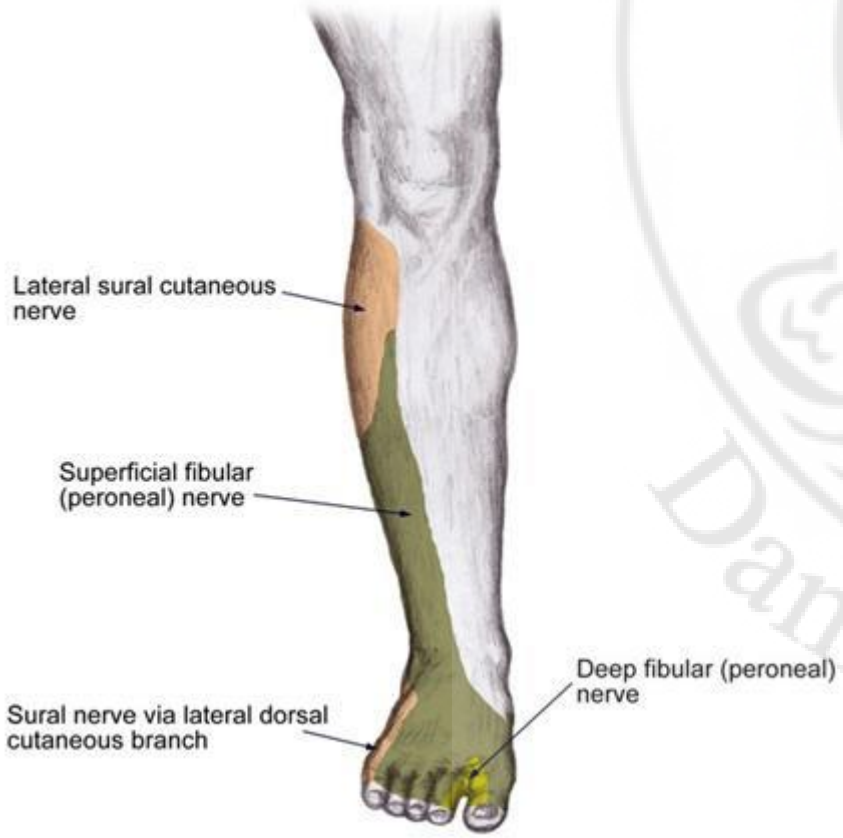


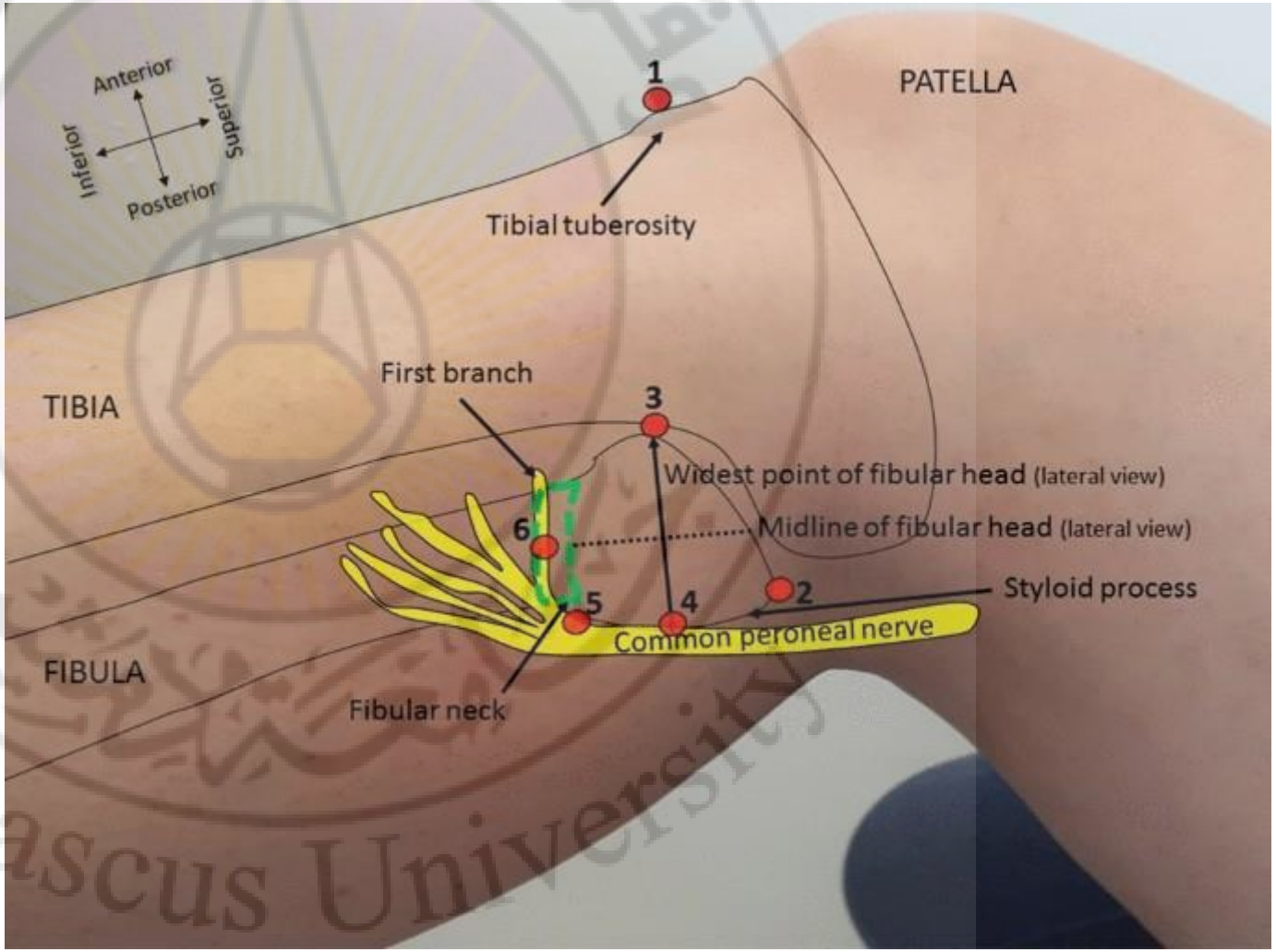


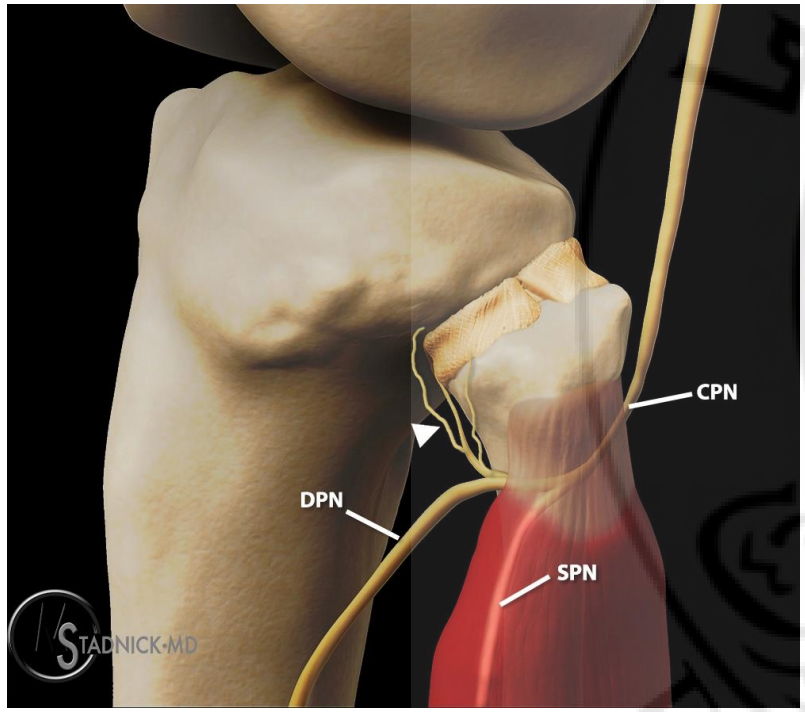


Peripheral nerve lesions

Peripheral nerve lesions



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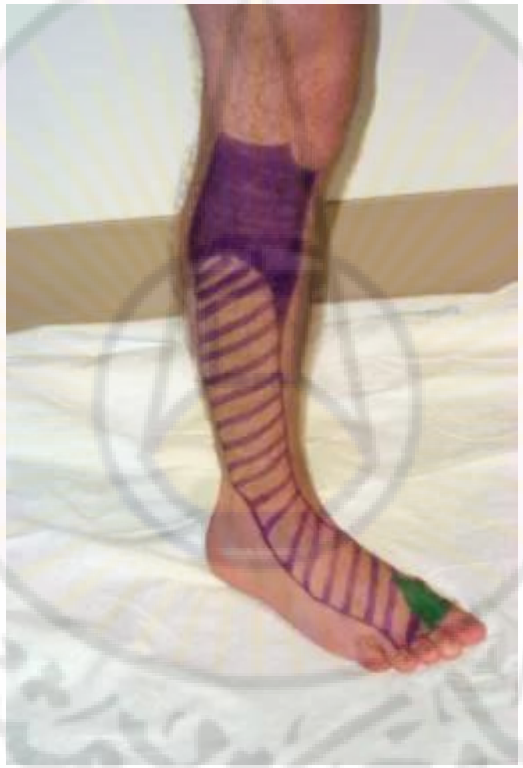
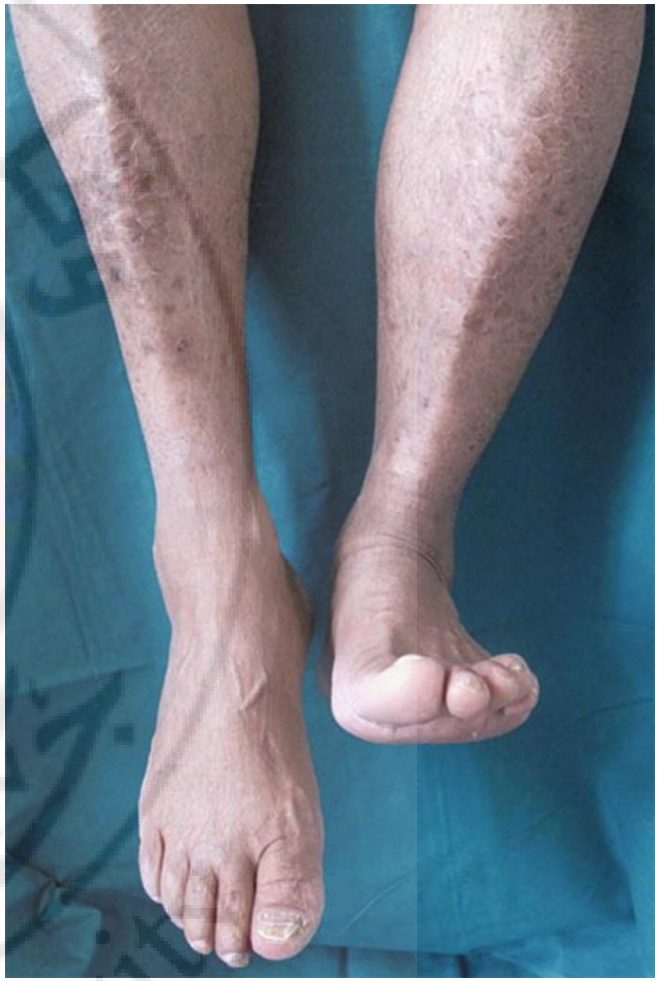
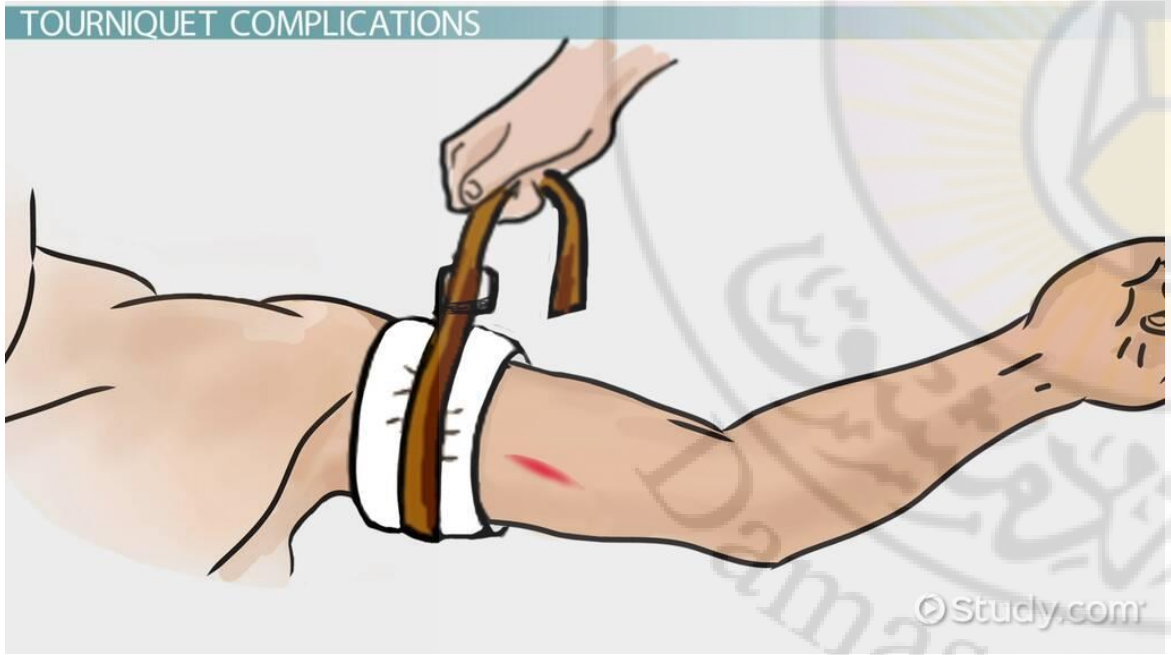




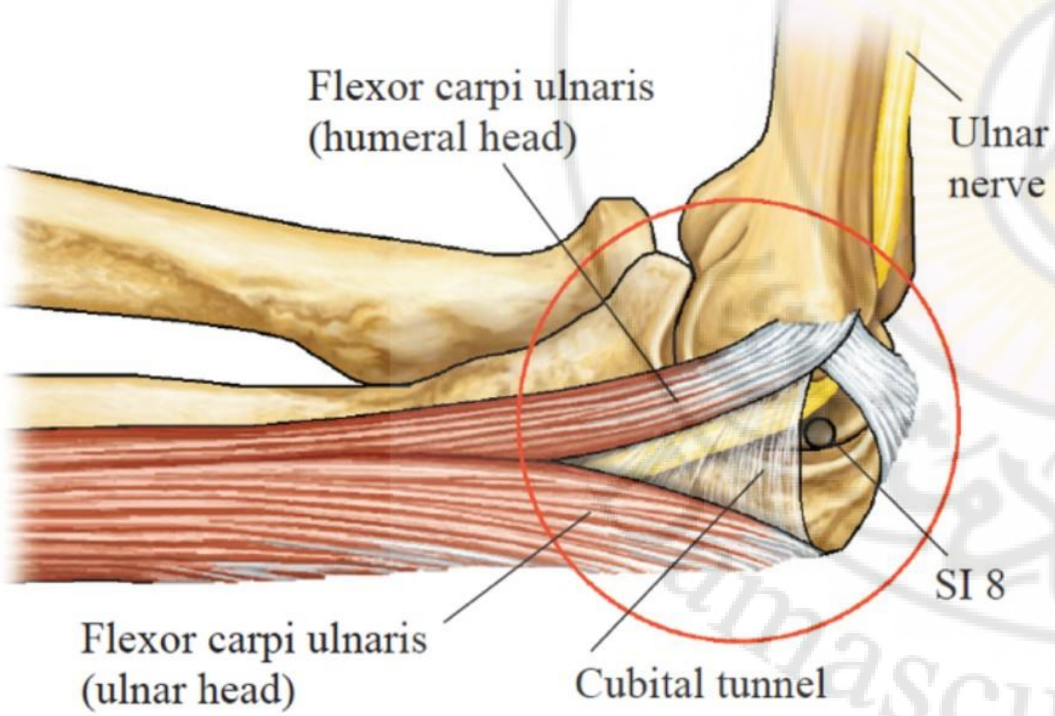
Nerve root lesions

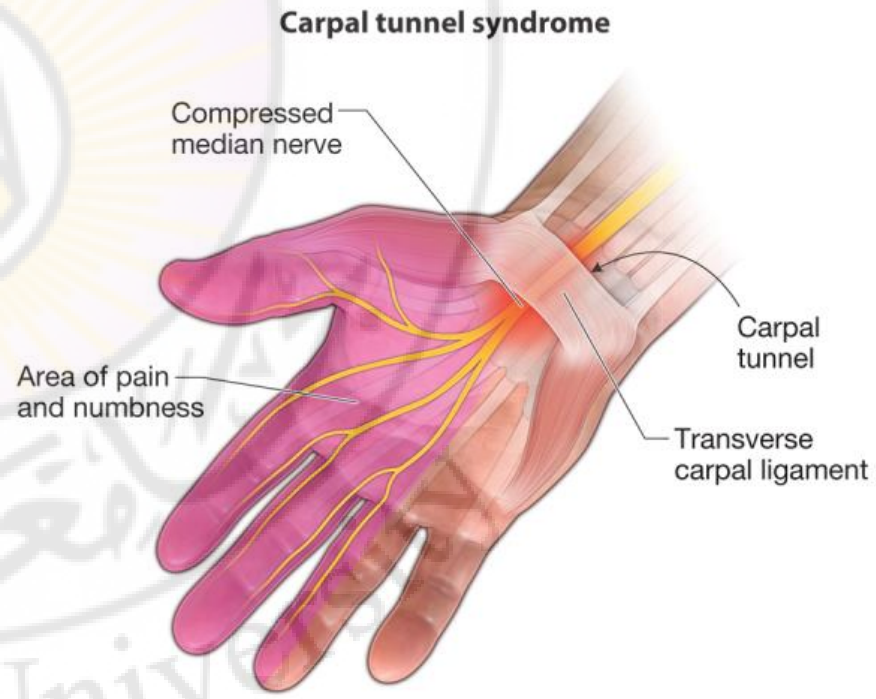
3. Iatrogenically: following prolonged tourniquet application (e.g. radial nerve in the arm), or as a result of an ill-fitting plaster cast (e.g. common peroneal nerve in the leg).



Peripheral nerve lesions

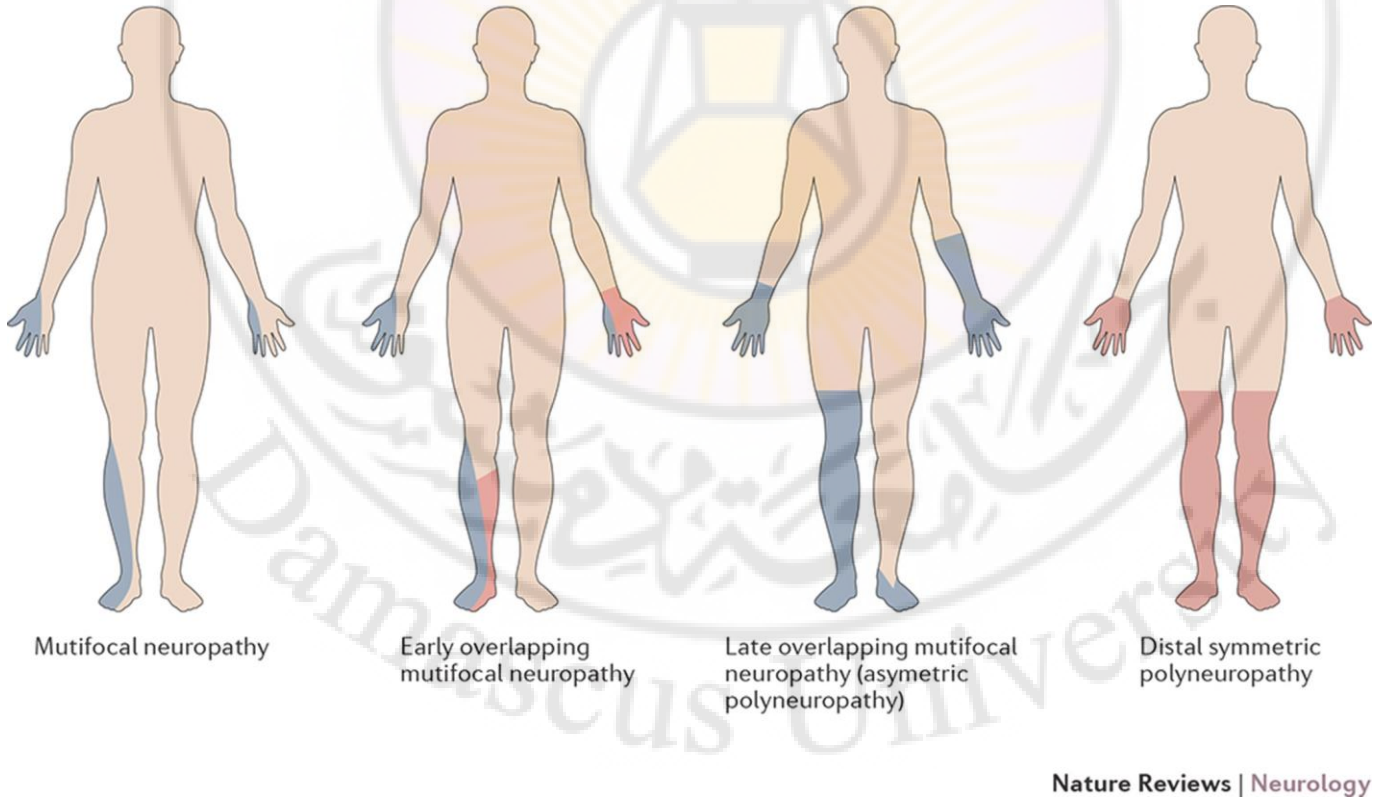
4. Chronic compression: so-called entrapment neuropathy, which occurs where nerves pass through confined spaces bounded by rigid anatomical structures, especially near to joints (e.g. ulnar nerve at the elbow or median nerve at the wrist).



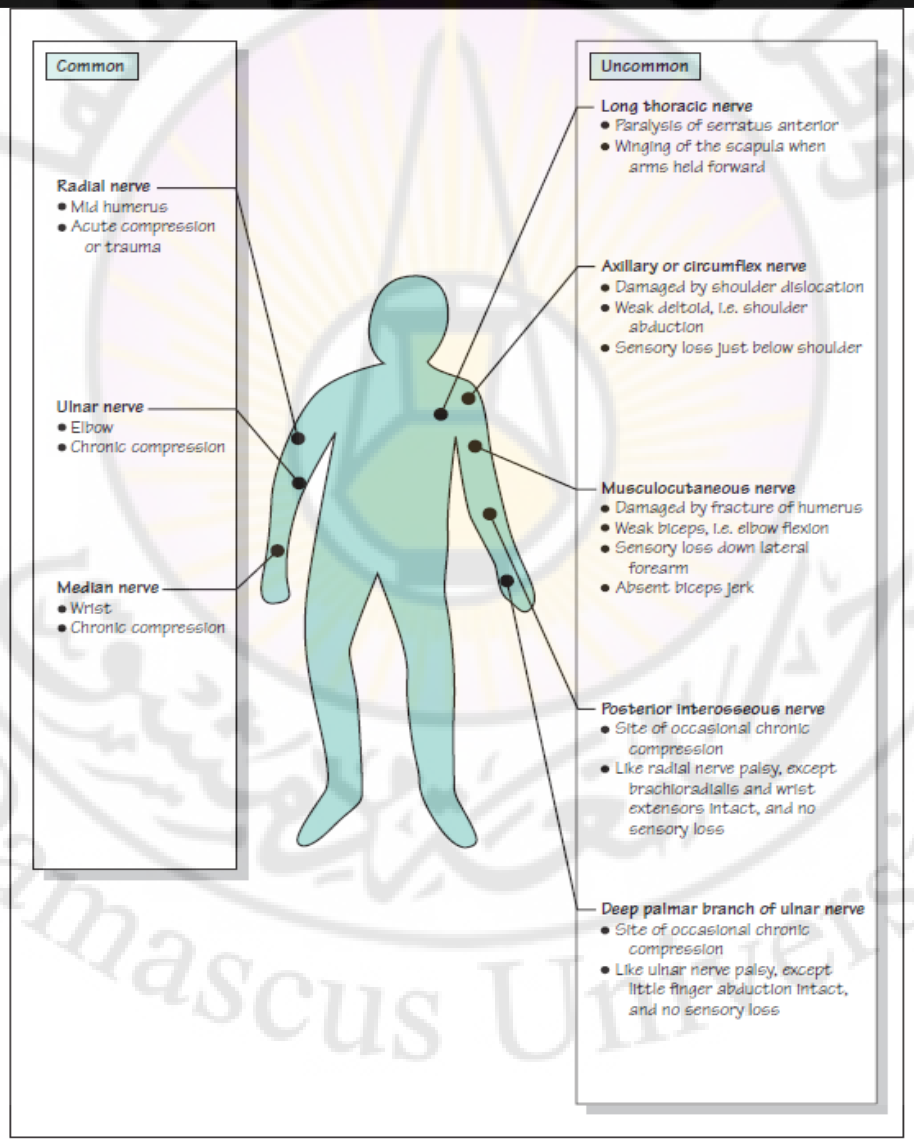


Peripheral nerve lesions

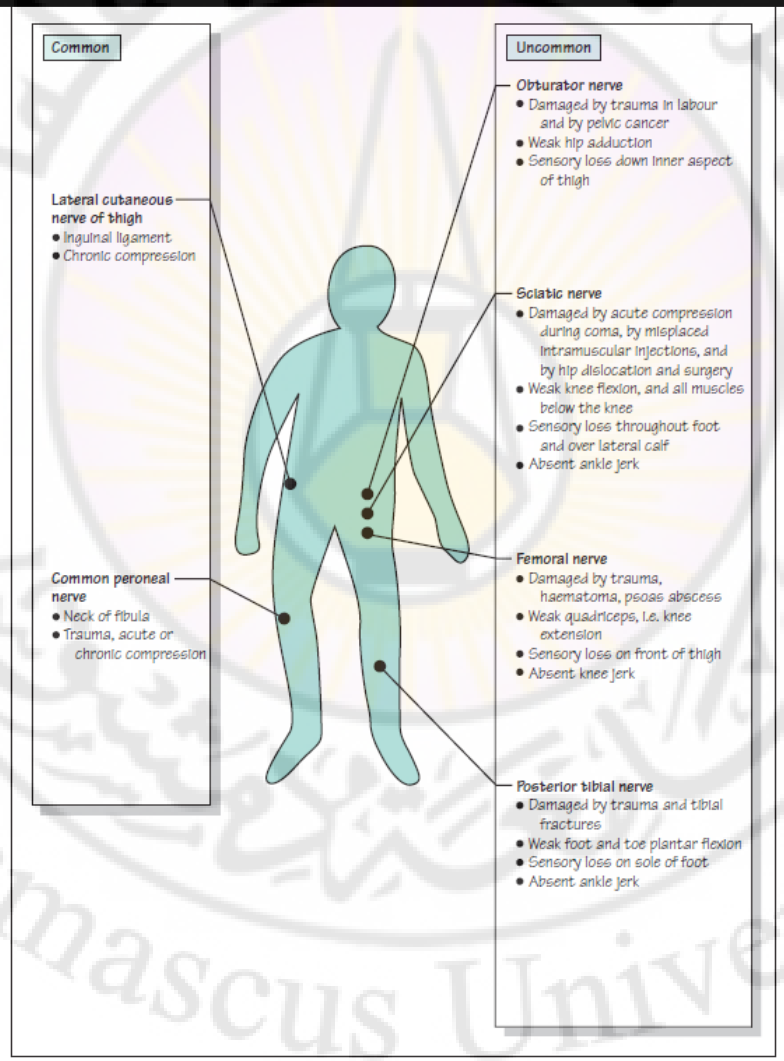
5. As part of the clinical picture of multifocal neuropathy. There are some conditions that can produce discrete focal lesions in individual nerves, so that the patient presents with more than one nerve palsy either simultaneously or consecutively (e.g. leprosy, diabetes and vasculitis).



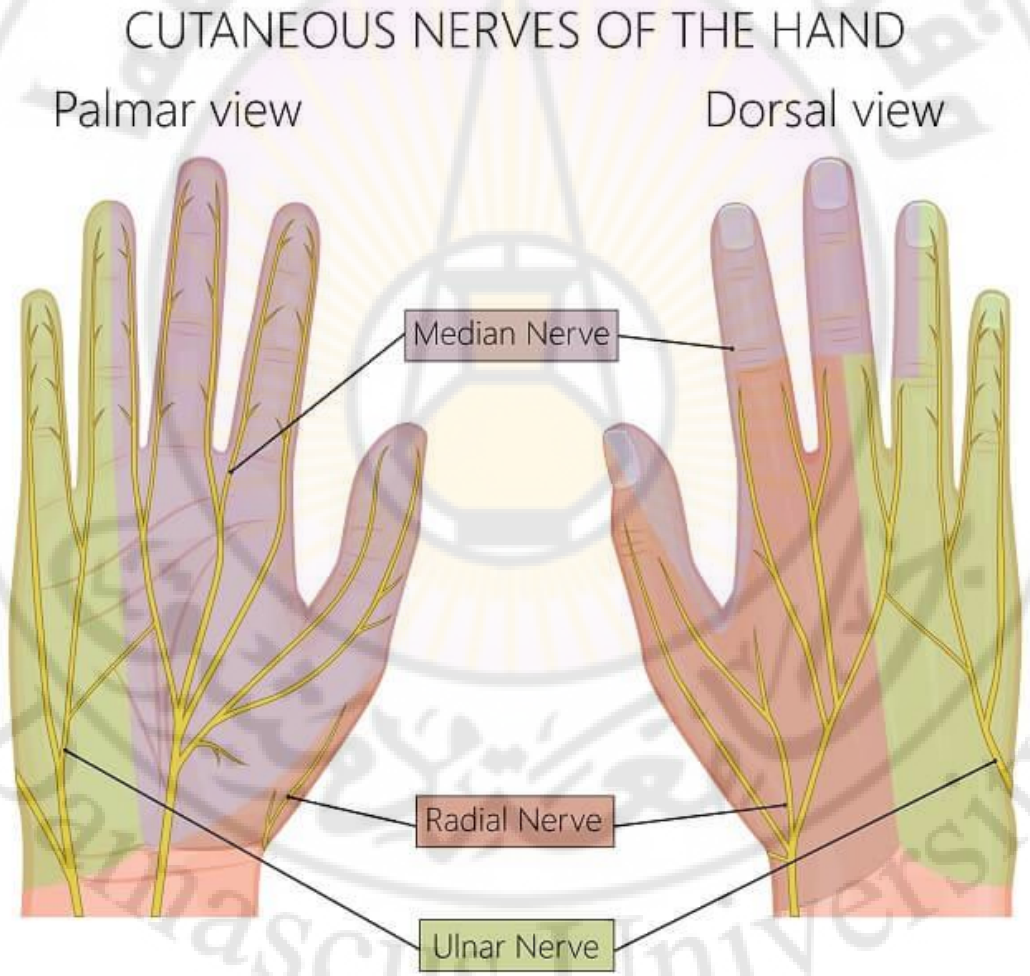
Peripheral nerve lesions



Peripheral nerve lesions



Peripheral nerve lesions



Peripheral nerve lesions

Motor loss

Brachioradialis
Wrist extensors
Finger extensors
Thumb extensors and abductor

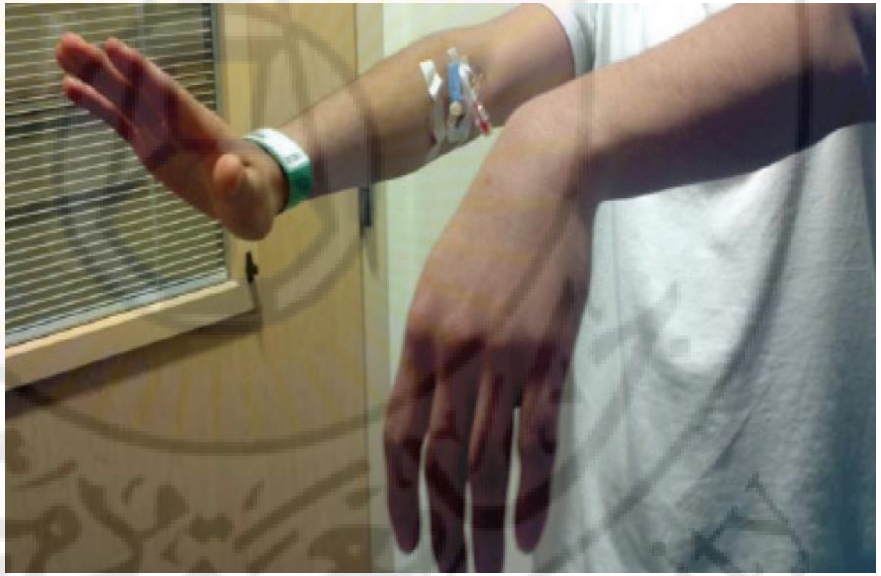
Reflex loss

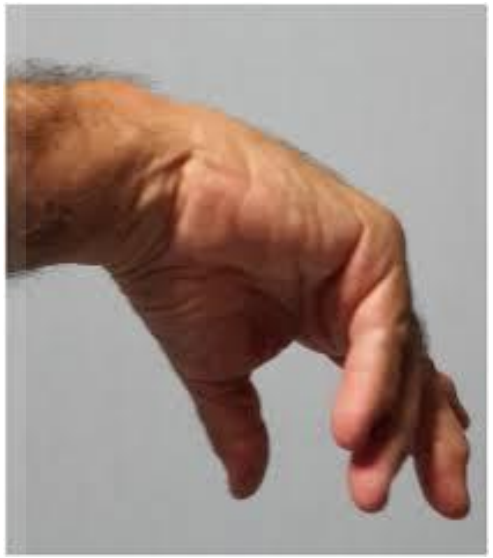
Absent brachioradialis (supinator) jerk

Sensory loss

Nerve sensitivity

Usually none





Radial nerve palsy.

Peripheral nerve lesions

Motor loss

Brachioradialis
Wrist extensors
Finger extensors
Thumb extensors
and abductor

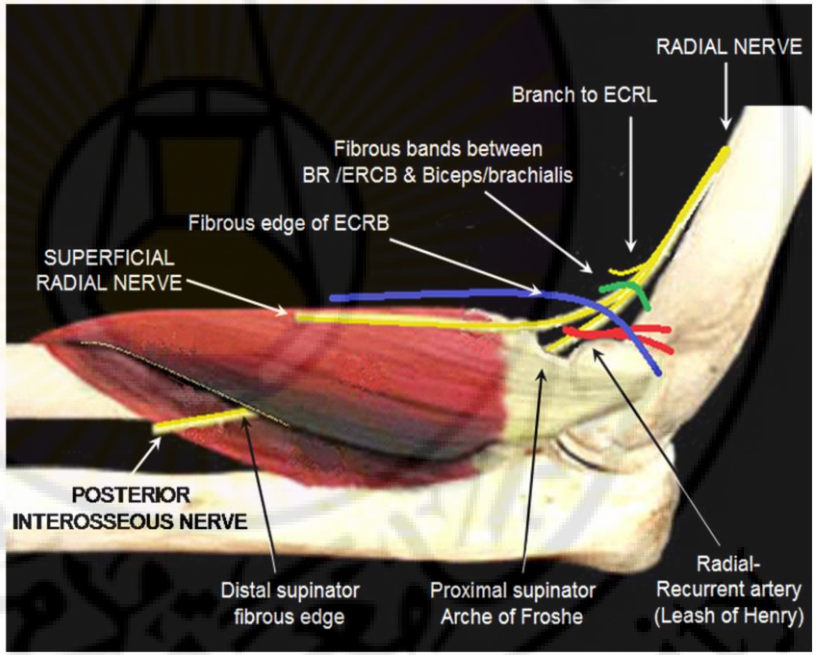
Reflex loss

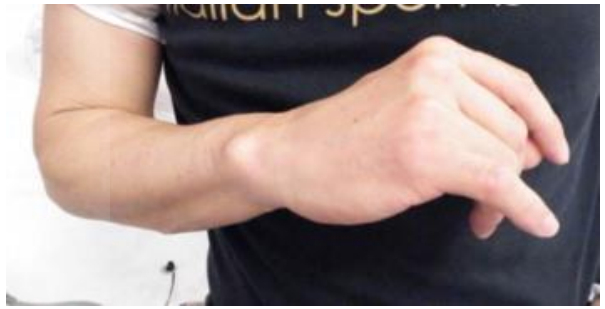
Absent brachioradialis (supinator) jerk

Sensory loss

Nerve sensitivity

Usually none





Radial nerve palsy.

Peripheral nerve lesions

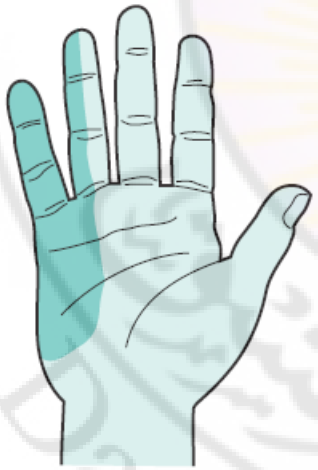
Motor loss

Flexor carpi ulnaris
Ulnar half of flexor digitorum profundus
All the small muscles of the hand except abductor pollicis brevis

Reflex loss

None

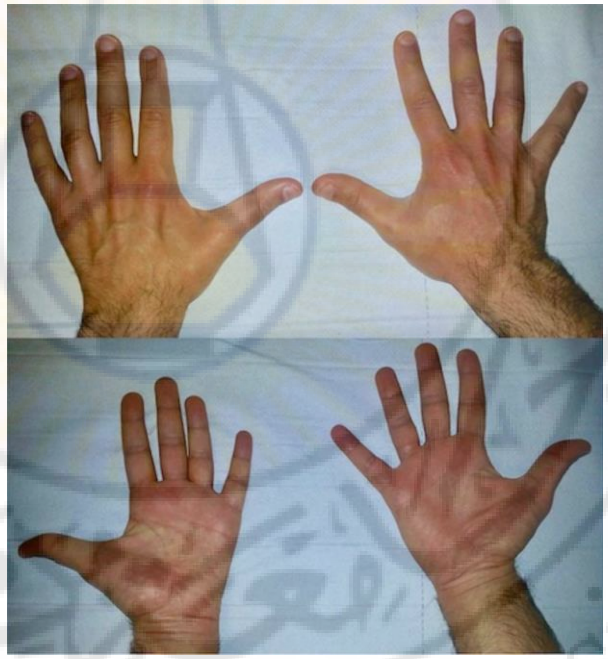
Sensory loss



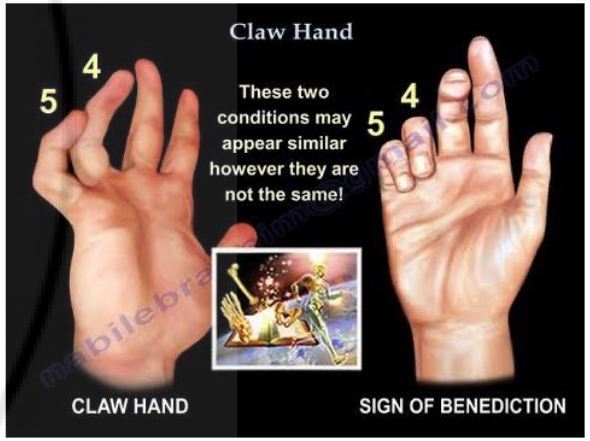
Nerve sensitivity

Often quite marked on the medial side of the elbow

Ulner nerve palsy.

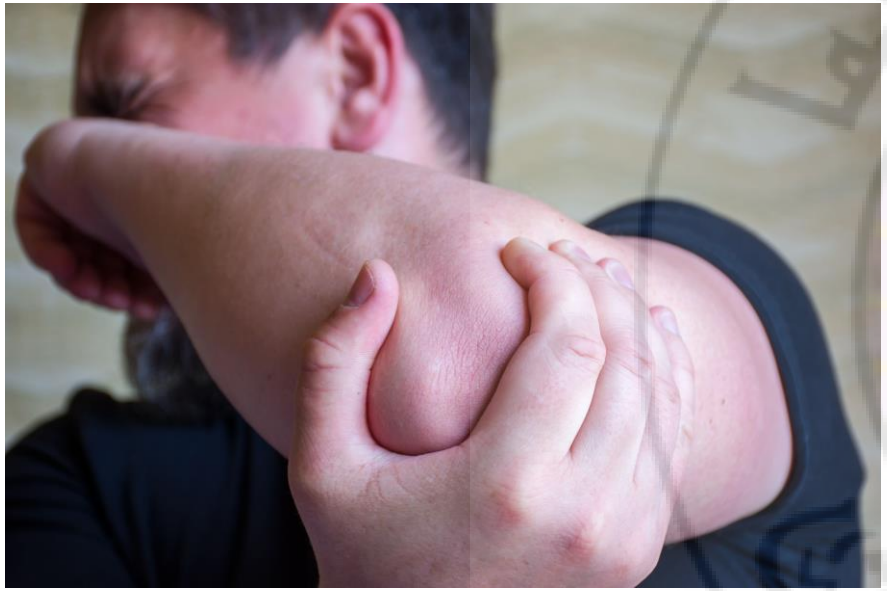


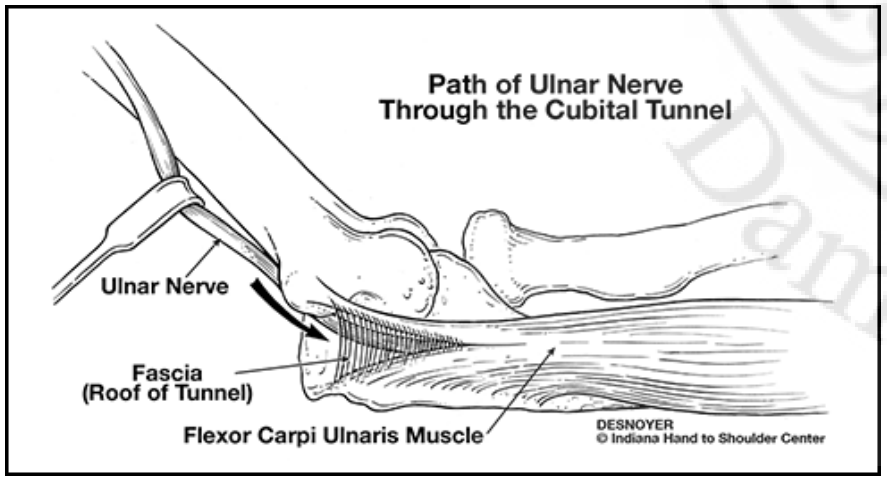
Ulnar Claw vs Hand of Benediction

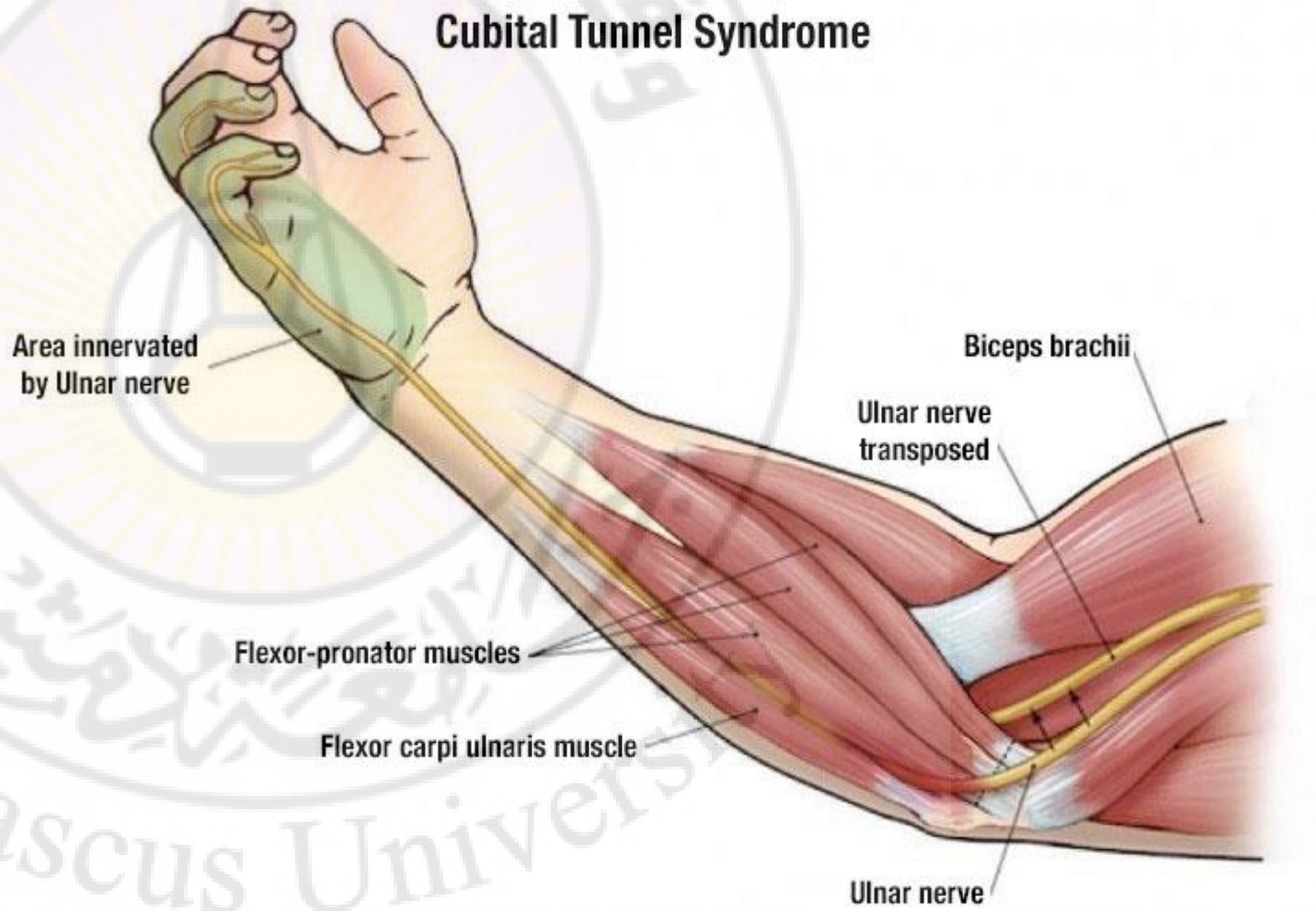


	Ulnar Claw	Hand of Benediction
Nerve Involved	Lesion of ulnar nerve at the wrist.	Lesion of the median nerve at the elbow or at the wrist.
Typical Presentation	Appears in long standing cases.	Appears when patient attempts to make a fist.
Digits Affected	Little and ring.	Middle and index.
Muscles Paralysed	• Medial two lumbricals	• Lateral two lumbricals • Lateral half of the FDP
Movements involved	Unopposed extension at the MCP Joints Unopposed flexion at the IP joints	***Inability*** to flex at the MCP and IP joints of the middle and index fingers ***Voluntary*** flexion at the MCP and IP joints of the ring and little fingers

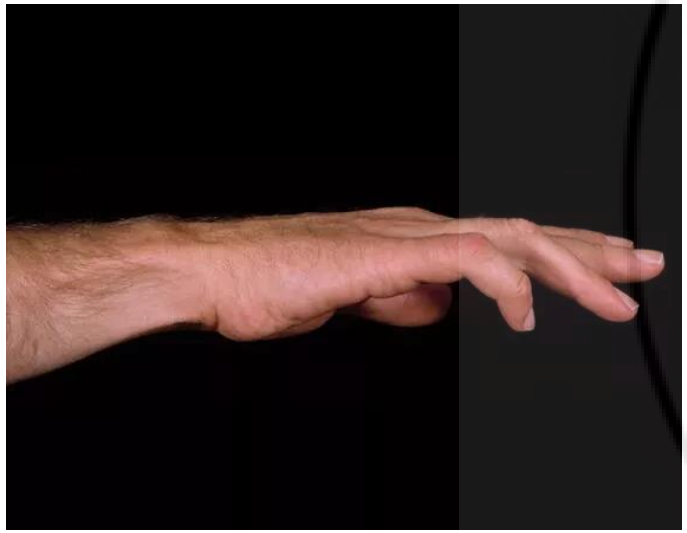
Peripheral nerve lesions

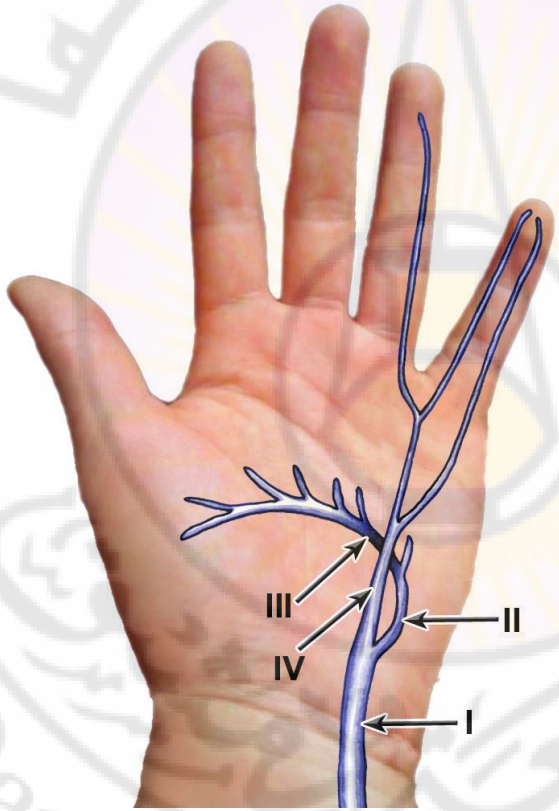


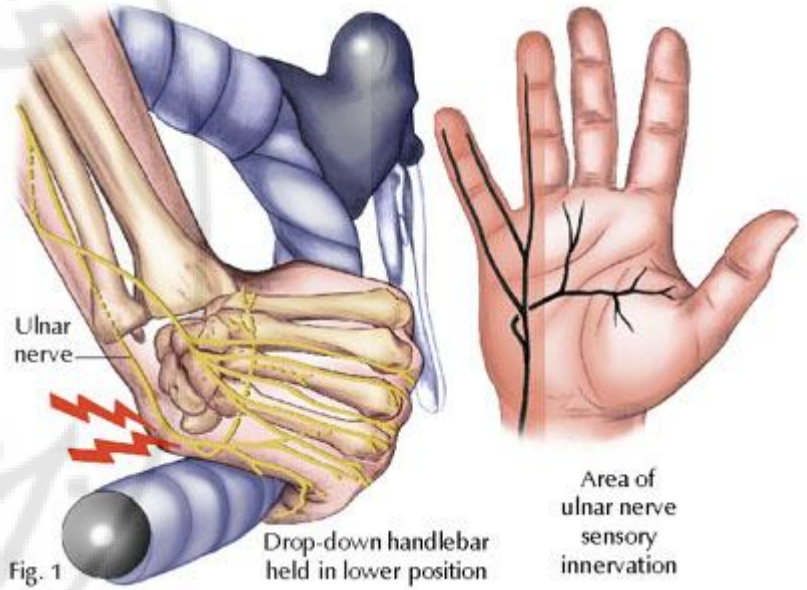




Peripheral nerve lesions







Classification of ulnar nerve's lesions within Guyon's canal — after Andreisek et al. I — ulnar nerve; II — proximal portion of deep branch of the ulnar nerve; III — middle fragment of the deep branch of ulnar nerve; IV — superficial branch of the ulnar nerve.

Peripheral nerve lesions

Motor loss

Abductor pollicis brevis

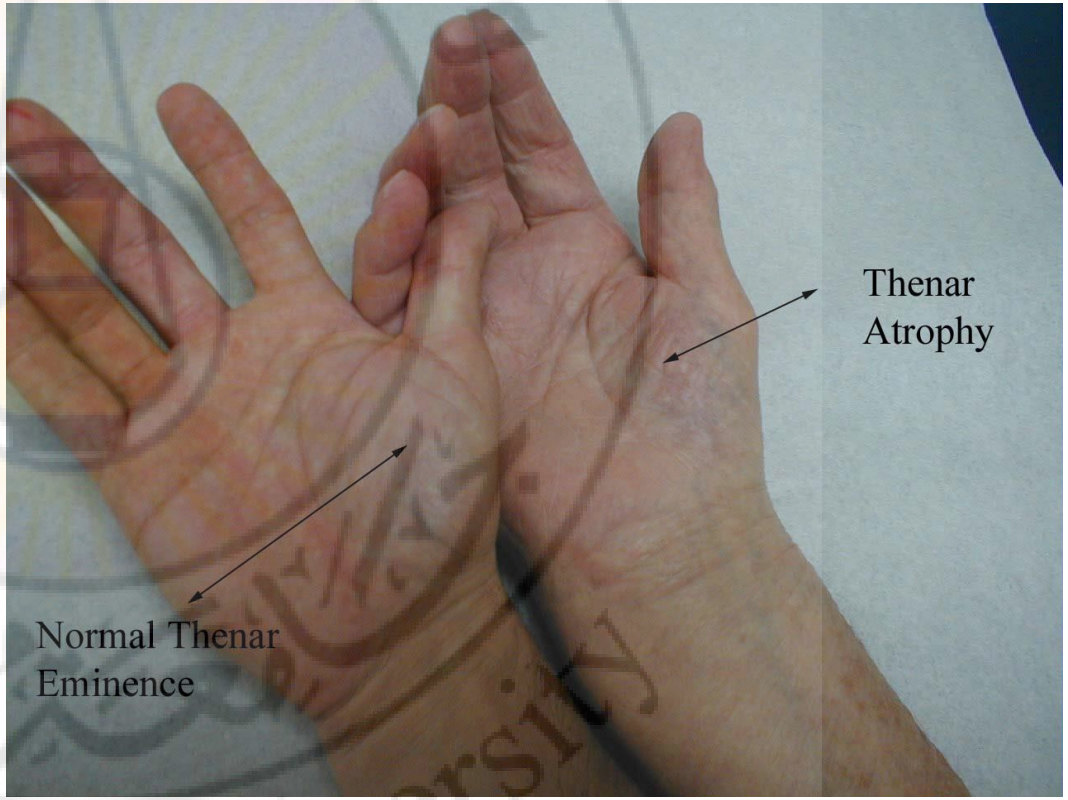
Reflex loss

None

Sensory loss

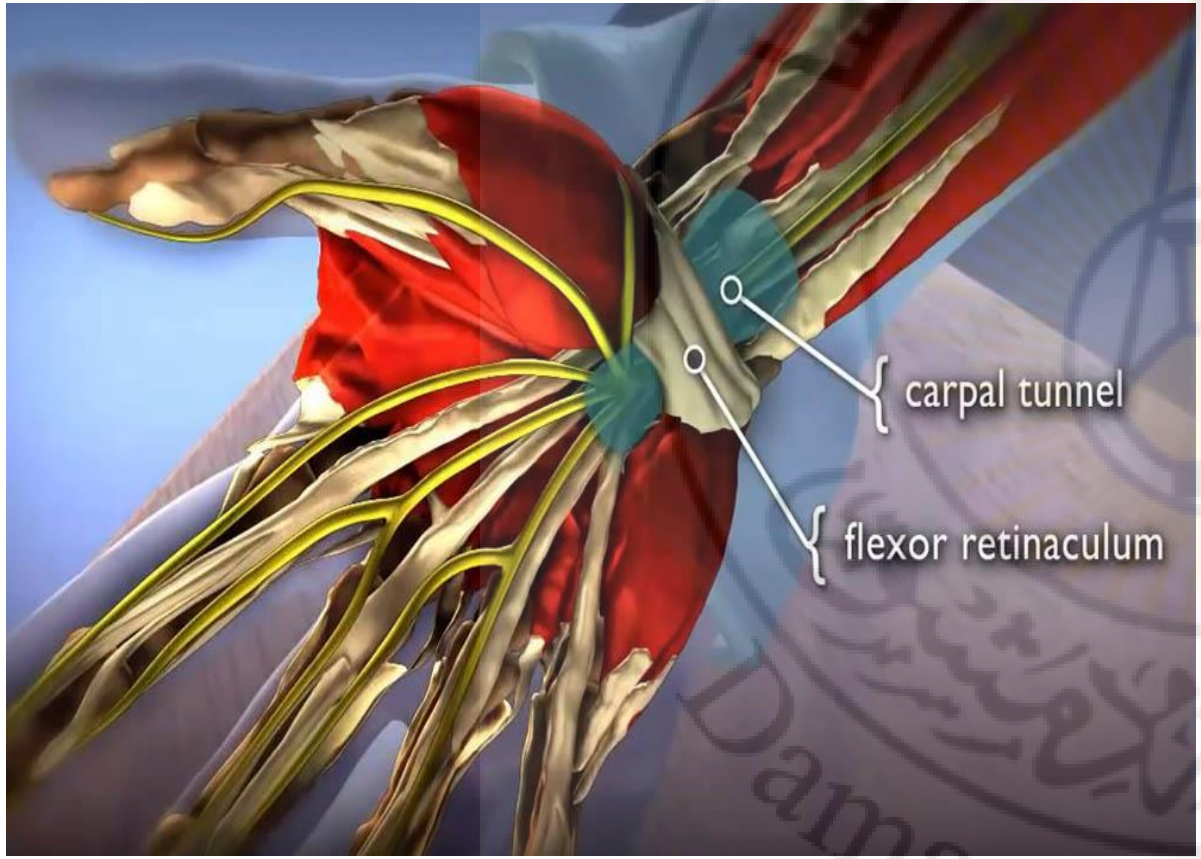
Nerve sensitivity

Sometimes at the level of the carpus

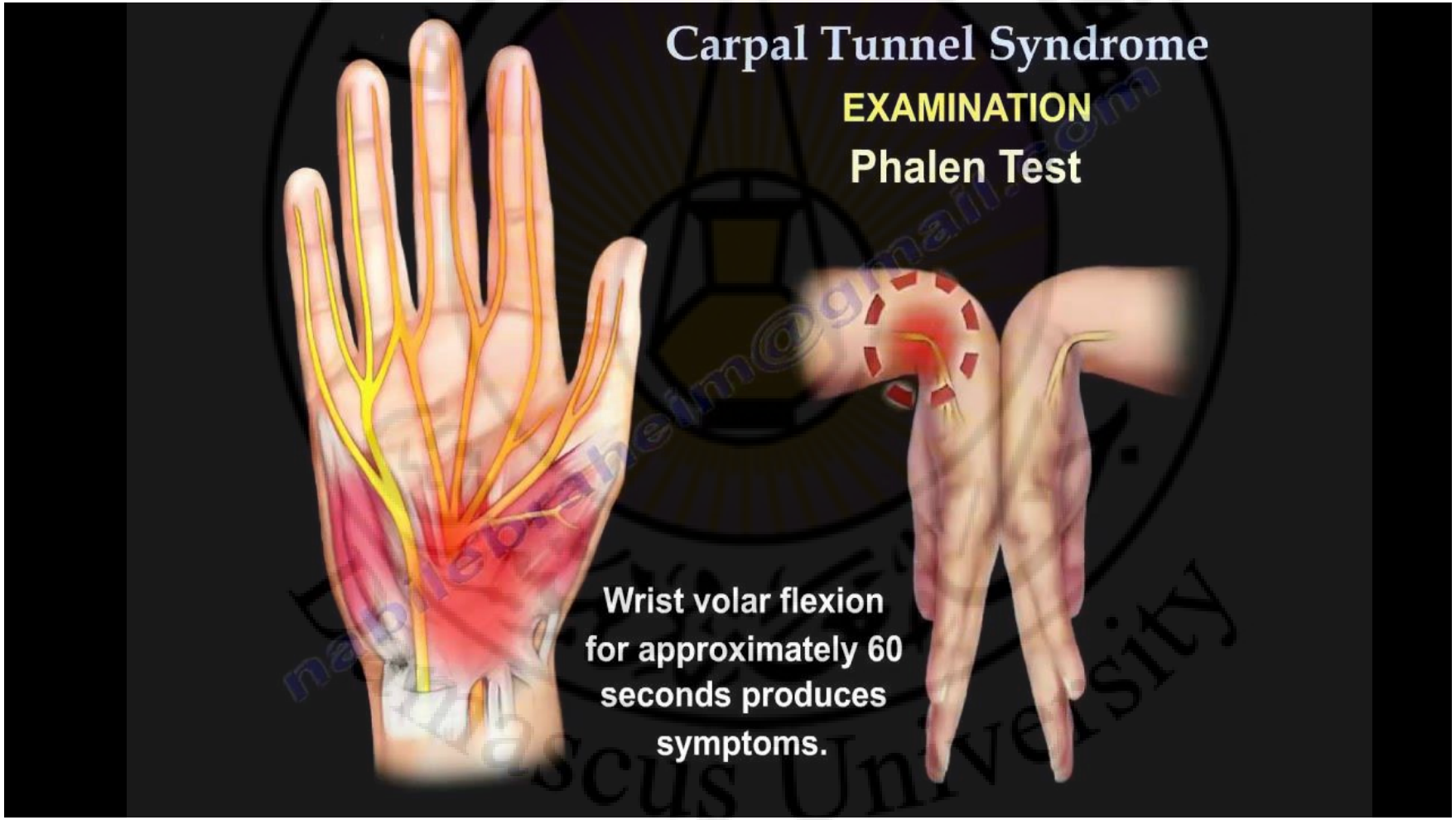


Median nerve palsy.

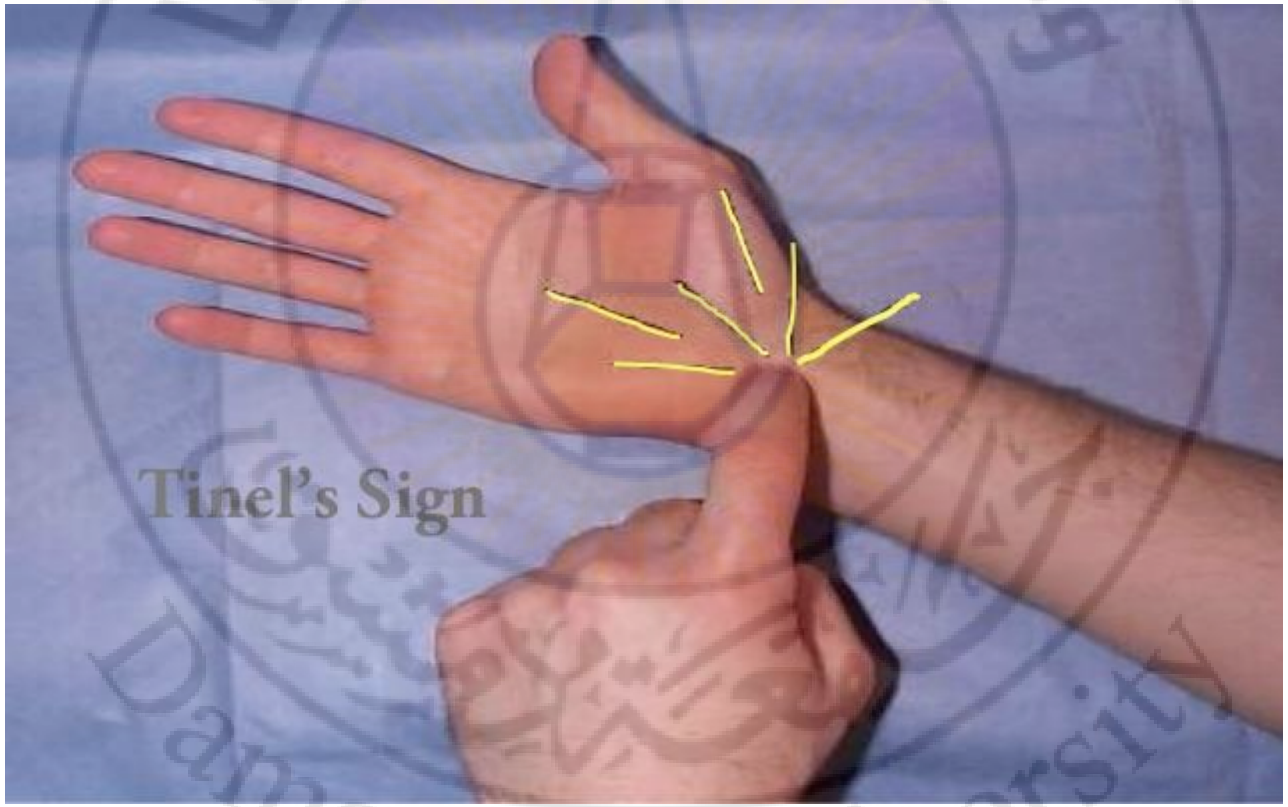
Peripheral nerve lesions



Peripheral nerve lesions



Peripheral nerve lesions



Peripheral nerve lesions

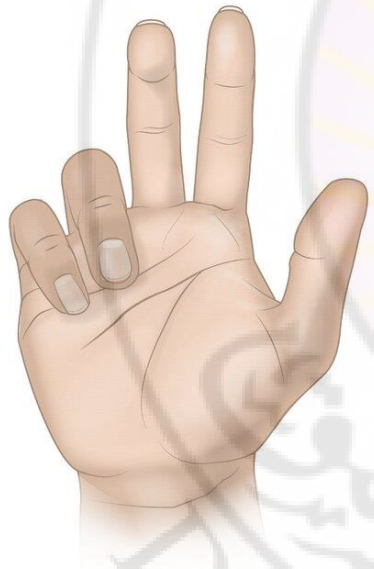
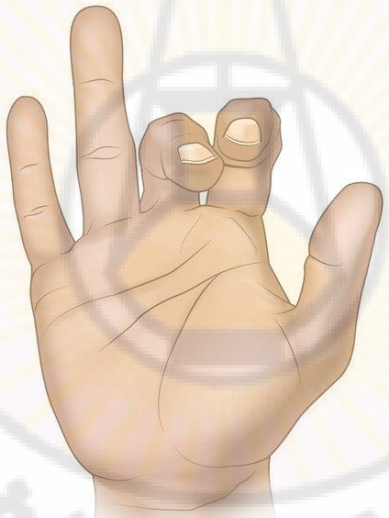
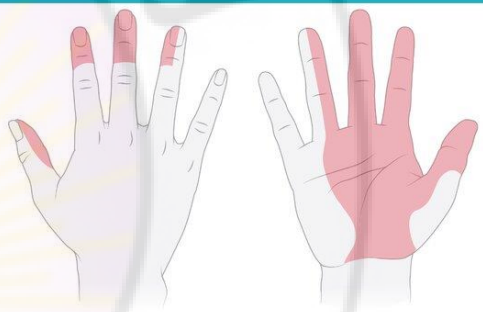
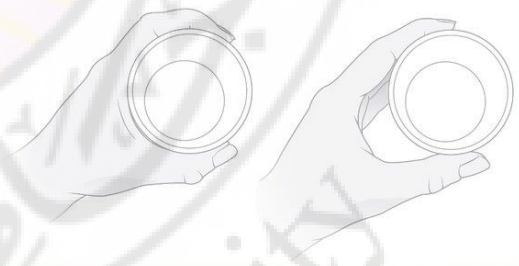
Carpal tunnel syndrome: causes

MEDIAN TRAP:

- **M**yxoedema
- **E**dema premenstrually
- **D**iabetes
- **I**diopathic
- **A**gromegaly
- **N**eoplasm
- **T**rauma
- **R**heumatoid arthritis
- **A**myloidosis
- **P**regnancy

*Mnemonic fits nicely since median nerve is trapped.

Peripheral nerve lesions

Proximal median nerve lesions (above AI nerve origin)	Distal median nerve lesions (below AI nerve origin)	Proximal and distal lesions
		 Sensory deficits 
Hand of benediction (Pope's blessing) *When patient tries to make a fist*	Median claw *When patient tries to extend fingers*	Normal Bottle sign *When patient holds cylindrical object*

Peripheral nerve lesions

Anterior interosseous syndrome

Hand posture in anterior interosseous syndrome due to paresis of flexor digitorum profundis and flexor pollicis longus mm.

Peripheral nerve lesions

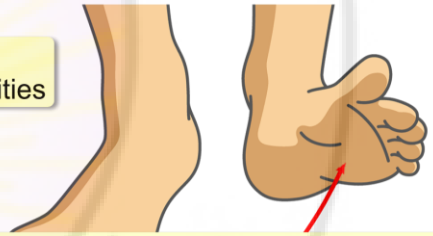
Motor loss	Reflex loss	Sensory loss
Foot evertors Foot dorsiflexors Toe dorsiflexors	None	

Nerve sensitivity

Sometimes at the neck of the fibula

General examination: no abnormalities

Other systems: no abnormalities



Neurological examination:

L/Lower Limb:

- Decreased dorsiflexion of ankle and eversion of toes; ankle inversion intact.
- Decreased sensation over front of left leg and dorsum of left foot
- High stepping gait
- Tinel sign at fibular head

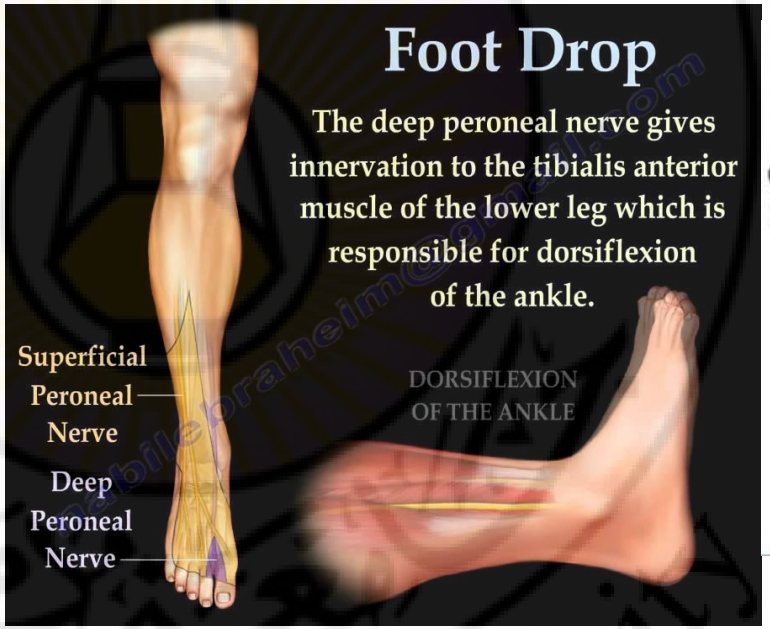
Common peroneal nerve palsy.

Peripheral nerve lesions

Motor loss	Reflex loss	Sensory loss
Foot evertors Foot dorsiflexors Toe dorsiflexors	None	

Nerve sensitivity

Sometimes at the neck of the fibula



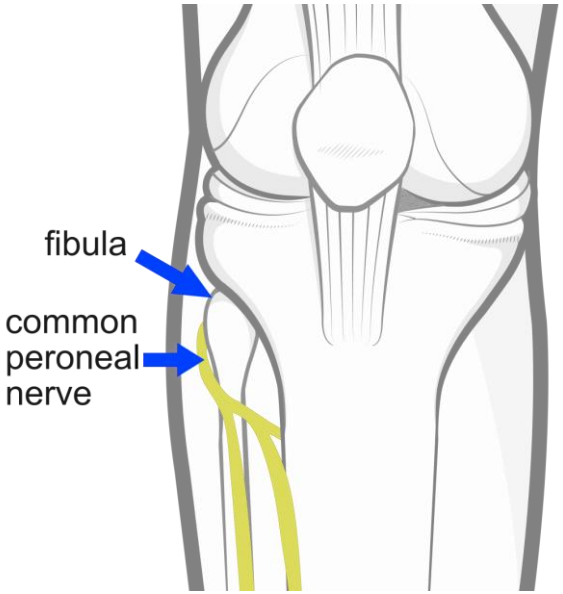
Common peroneal nerve palsy.

Peripheral nerve lesions

Motor loss	Reflex loss	Sensory loss
Foot evertors Foot dorsiflexors Toe dorsiflexors	None	

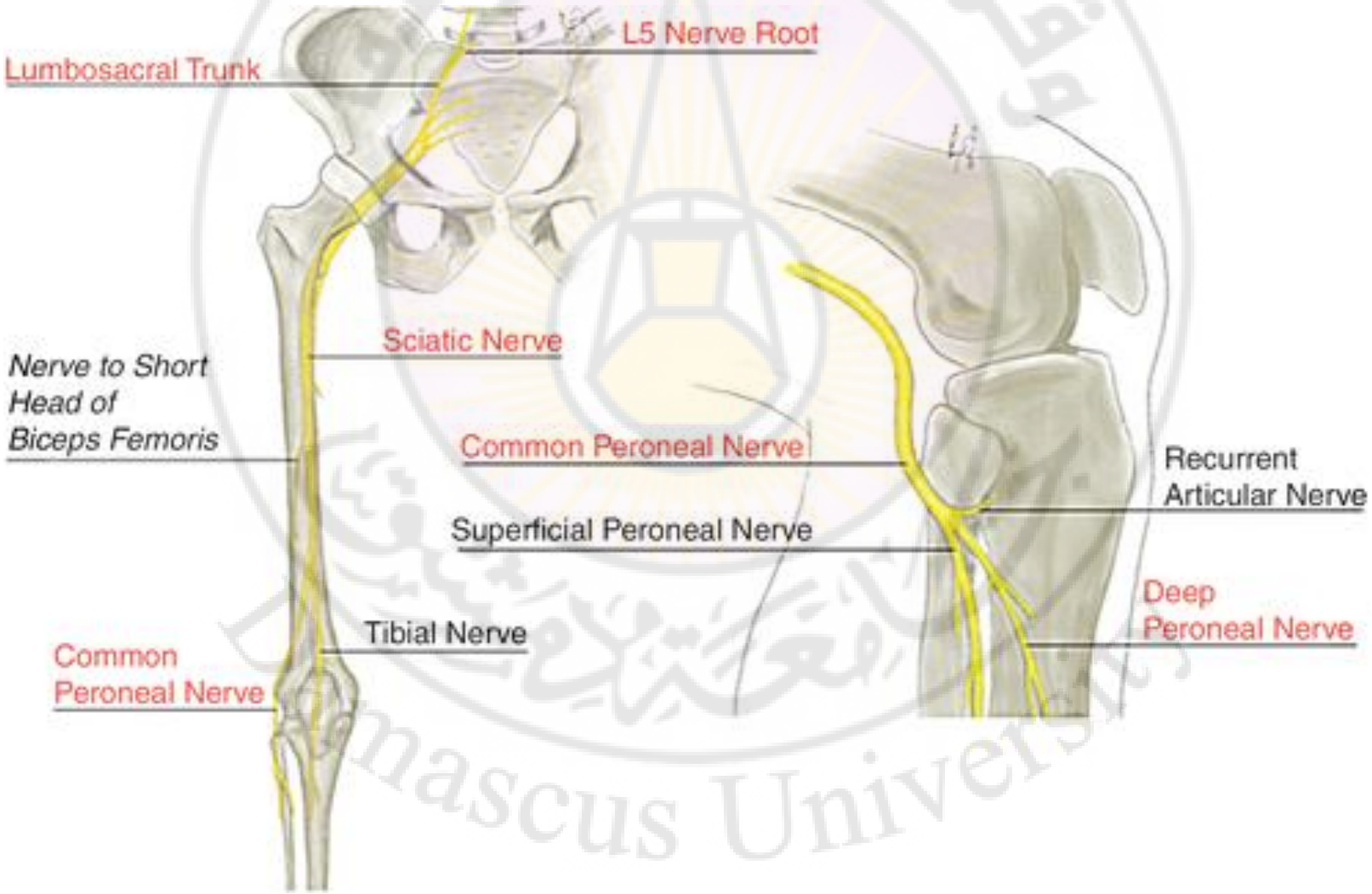
Nerve sensitivity

Sometimes at the neck of the fibula

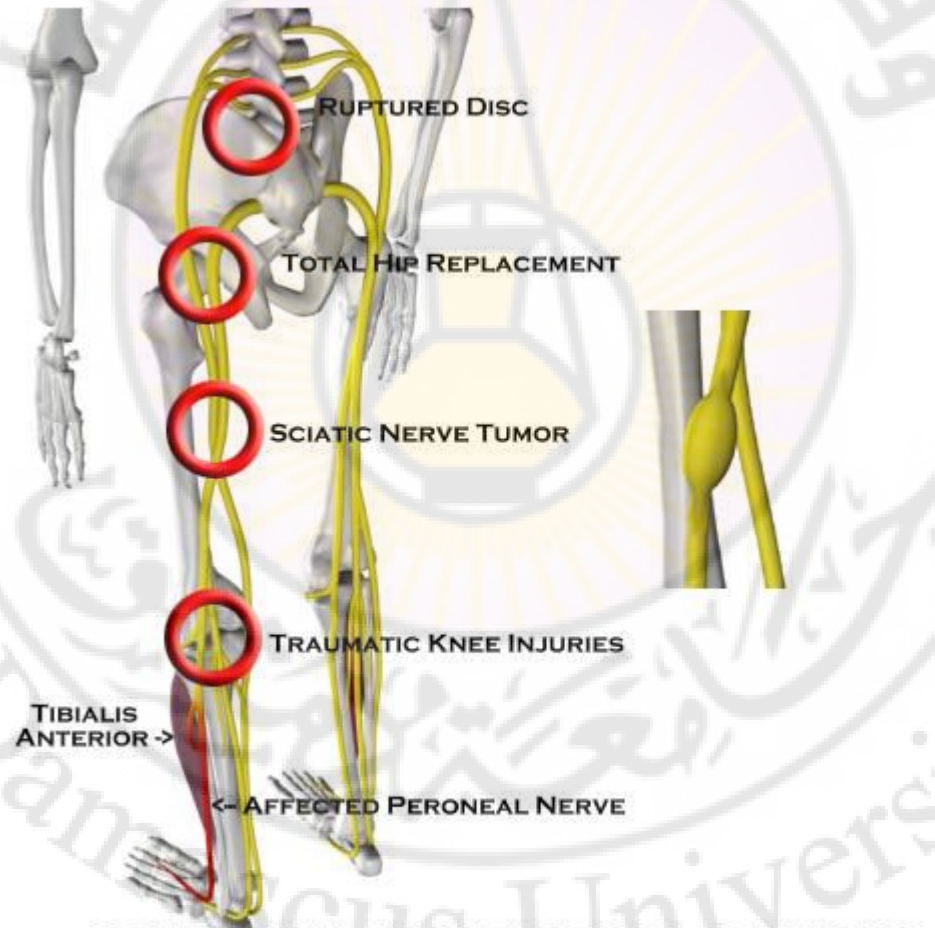


Common peroneal nerve palsy.

Peripheral nerve lesions

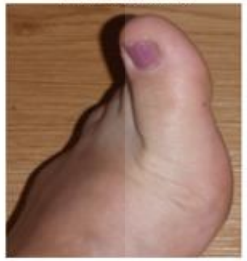
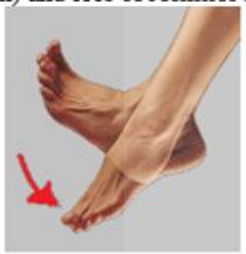


Peripheral nerve lesions



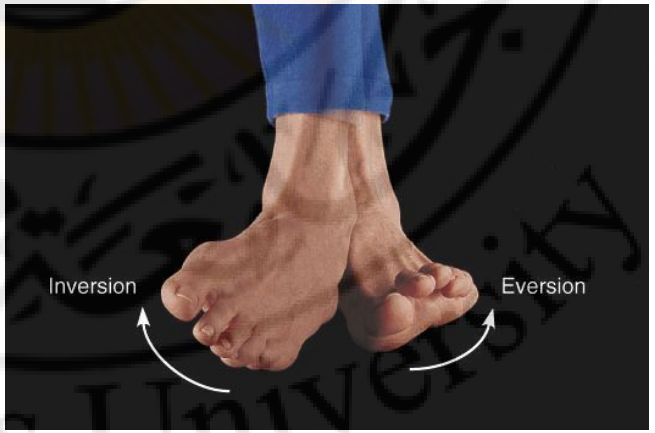
COMMON FOOT DROP CAUSES

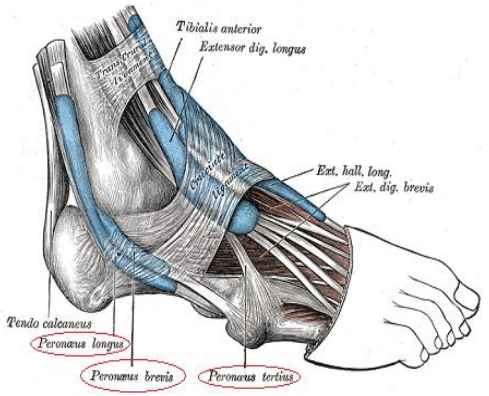
Peripheral nerve lesions

Nerve root	Motor	Sensory *(Figure 1)*
L4	Leg extension (quadriceps) 	Medial knee and shin sensory loss with pain down anterior thigh
L5	Extensor hallucis longus (big toe extension), hip abduction, and ankle dorsiflexion 	Sensory loss in big toe and pain down back of thigh and lateral gastrocnemius
S1	Gastrocnemius (ankle plantar flexion) and loss of Achilles reflex 	Sensory loss of lateral foot and pain down back of calf

L5 Radiculopathy vs Peroneal Nerve Injury

	Foot Drop?	Able to Invert Foot?	Able to Evert Foot?
L5 Radiculopathy	YES	NO	NO
Peroneal Nerve Injury	YES	YES	NO



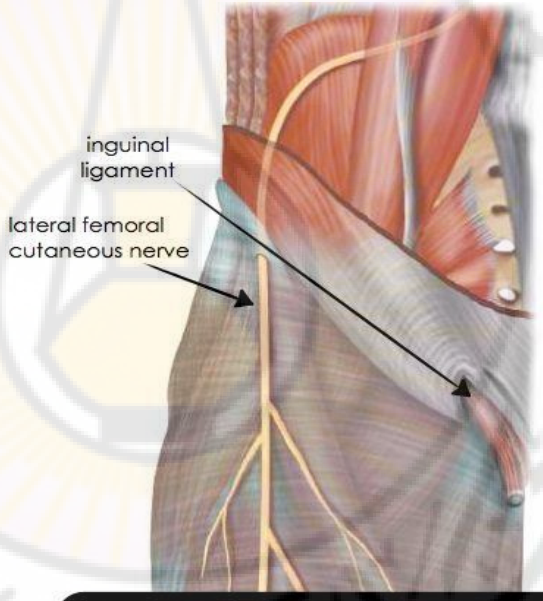


Peripheral nerve lesions

Motor loss	Reflex loss	Sensory loss
None	None	

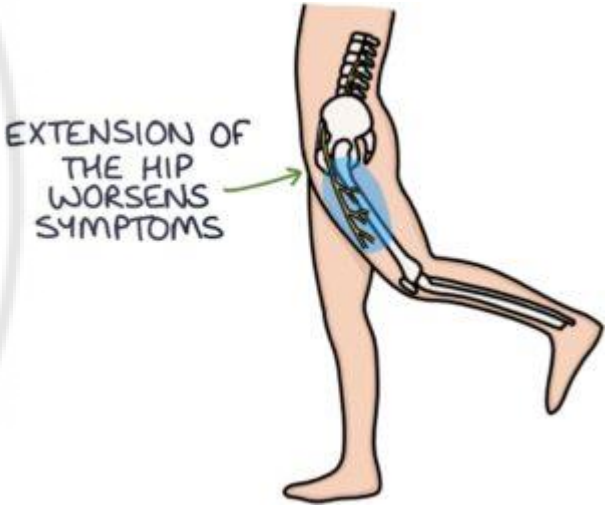
Nerve sensitivity

Usually none



Meralgia Paresthetica

- Pain and dysesthesias of the proximal, anterolateral thigh
- Compression of lateral femoral cutaneous nerve
- Entrapment under the inguinal ligament



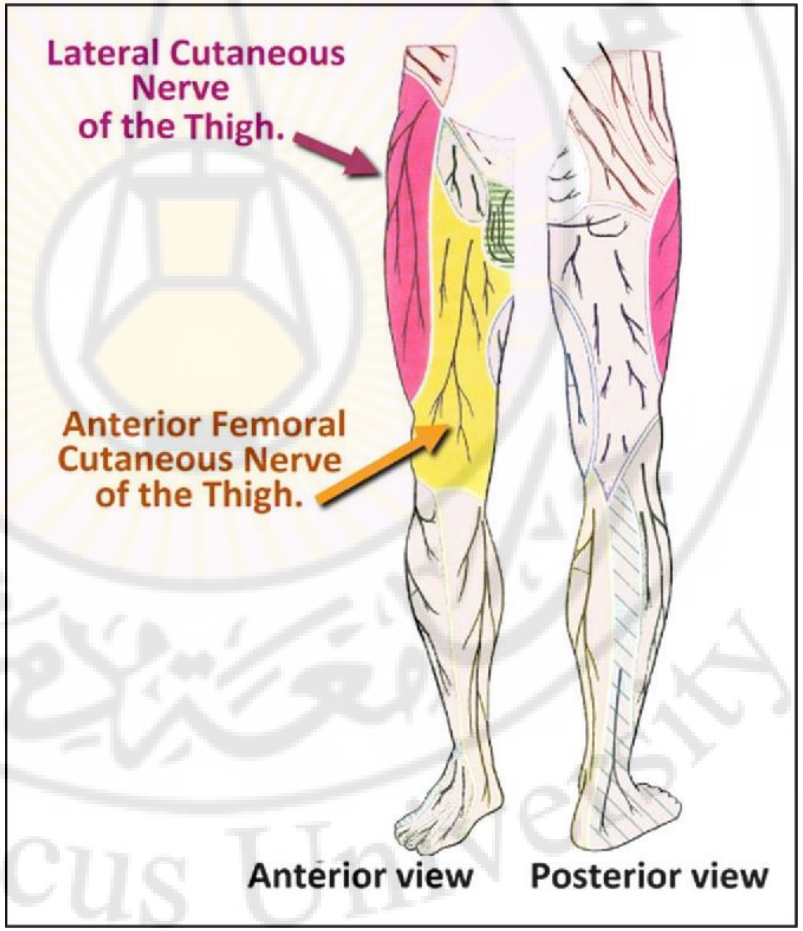
Lateral cutaneous nerve of the thigh.

Peripheral nerve lesions

Motor loss	Reflex loss	Sensory loss
None	None	

Nerve sensitivity

Usually none



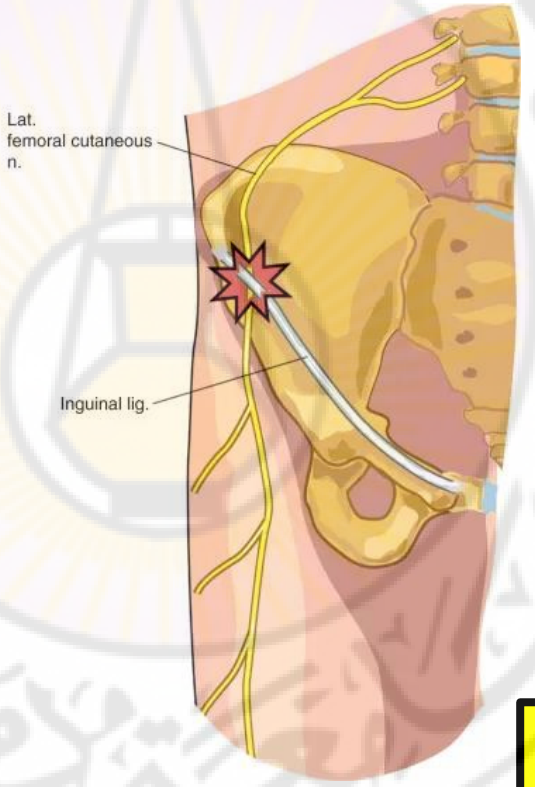
Lateral cutaneous nerve of the thigh.

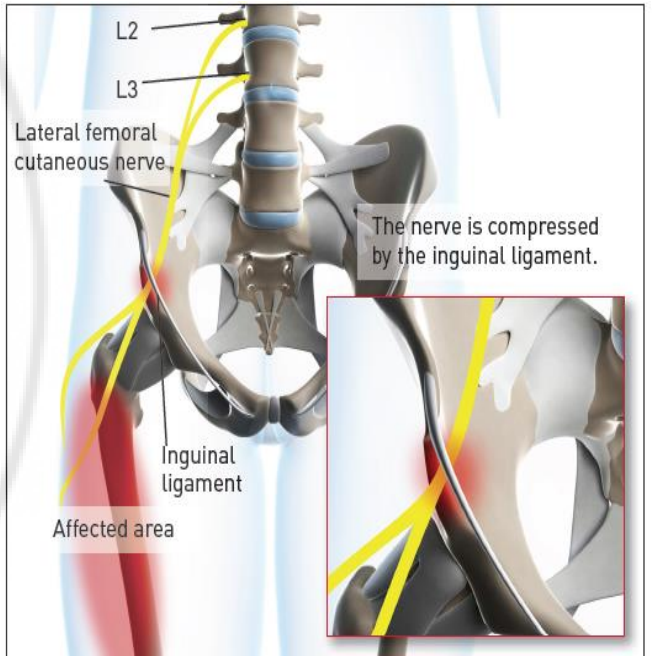
Peripheral nerve lesions

Motor loss	Reflex loss	Sensory loss
None	None	

Nerve sensitivity

Usually none



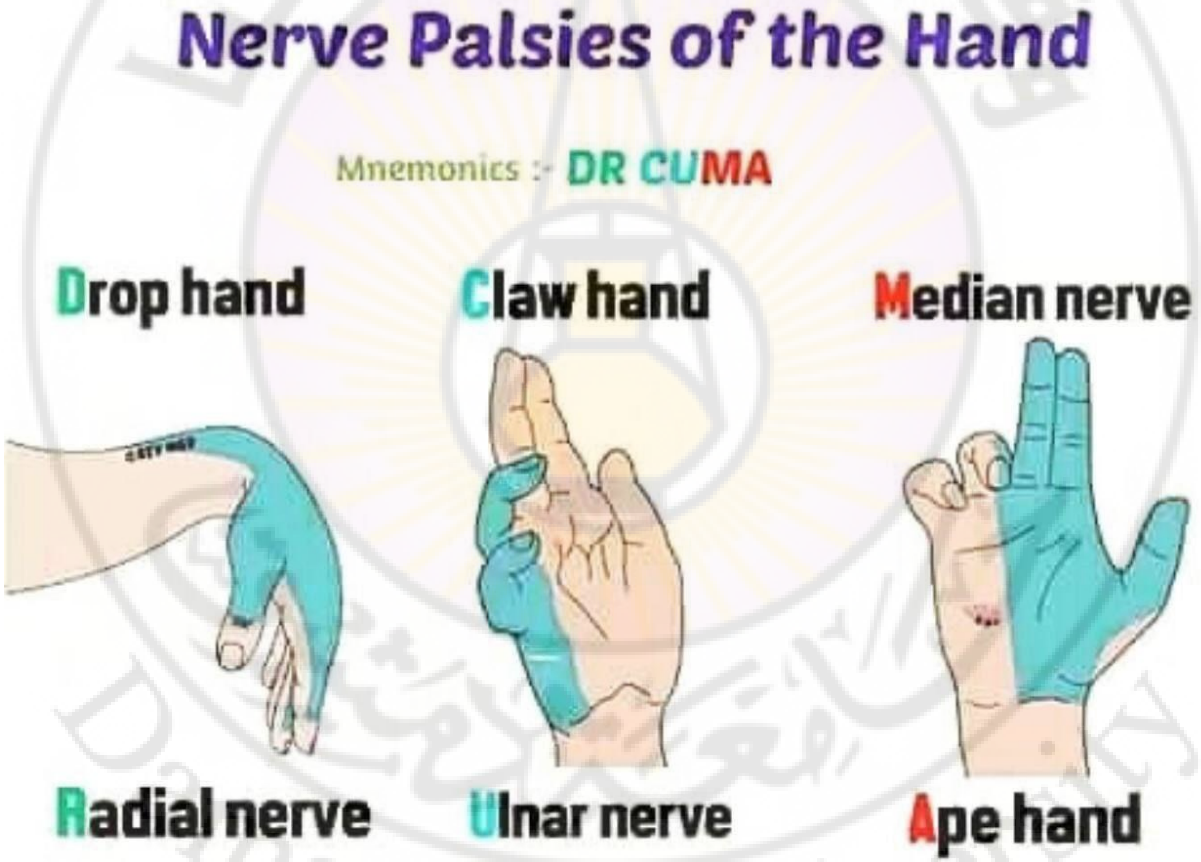


Lateral cutaneous nerve of the thigh.

Causes of meralgia paresthetica

- **Repetitive motion of the legs.**
- **Recent injuries to the hip.**
- **Wearing tight clothing or heavy belts.**
- **Weight gain.**

Peripheral nerve lesions



Radiculopathy vs Neuropathy

Radiculopathy

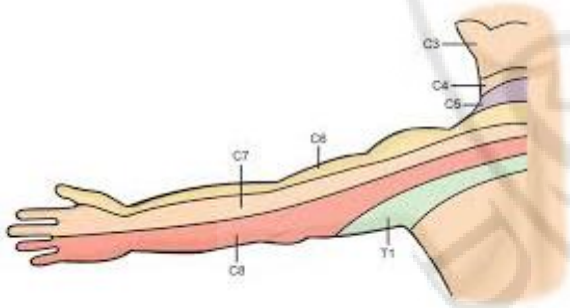
One spinal nerve root

Pathology proximal disc or osteophyte

Neuropathy

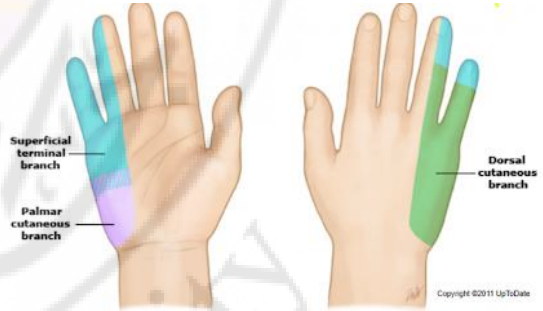
One peripheral nerve

Pathology distal entrapment



Double Crush Syndrome

Both Radiculopathy and Neuropathy



Peripheral nerve lesions

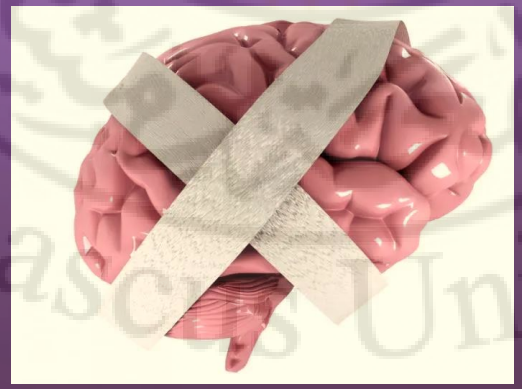
"Peace sign" against resistance	Ulnar nerve	
"Hitchhiker" / Thumbs up	Radial nerve	
"Power to the people"	Median nerve	
OK sign	Median nerve (anterior interosseous)	

بسم الله الرحمن الرحيم

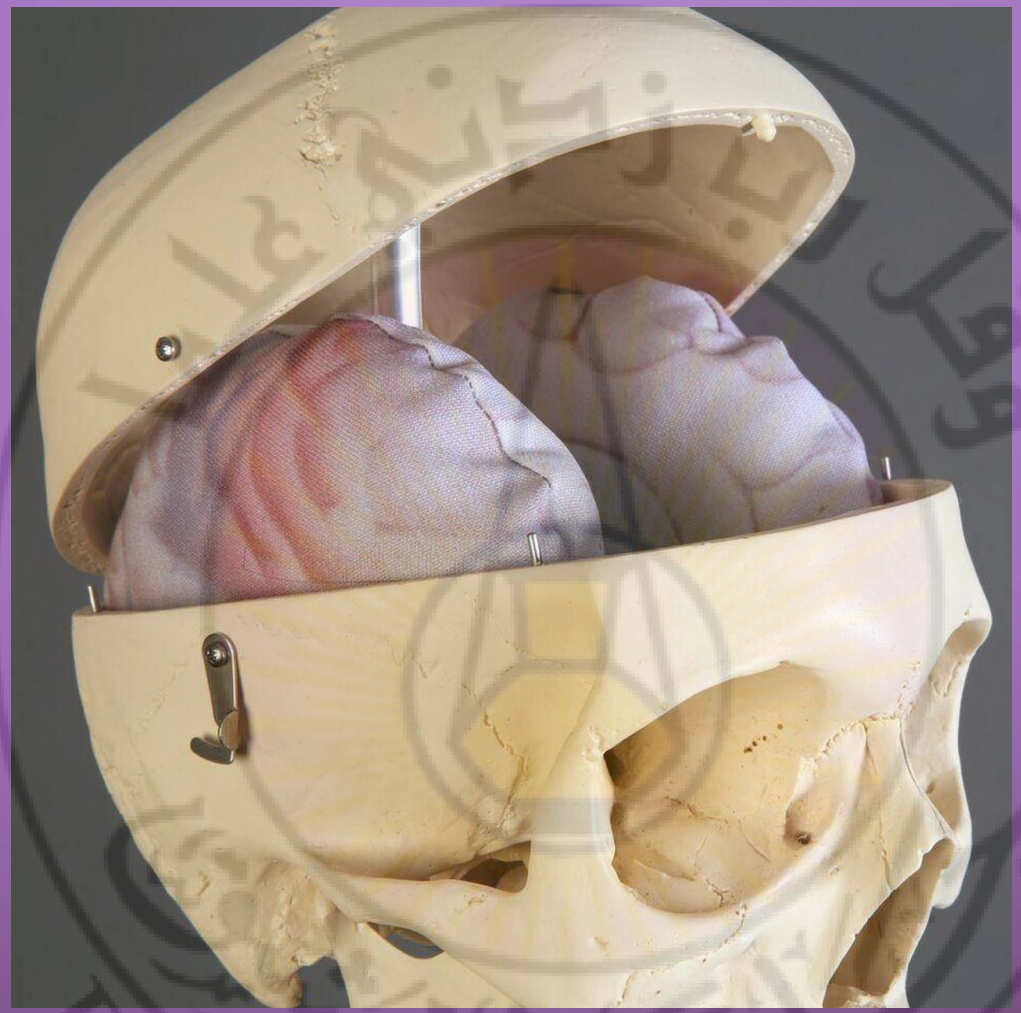
TRAUMATIC BRAIN INJURY

PROF. MOHAMAD SHEHADEH AGHA

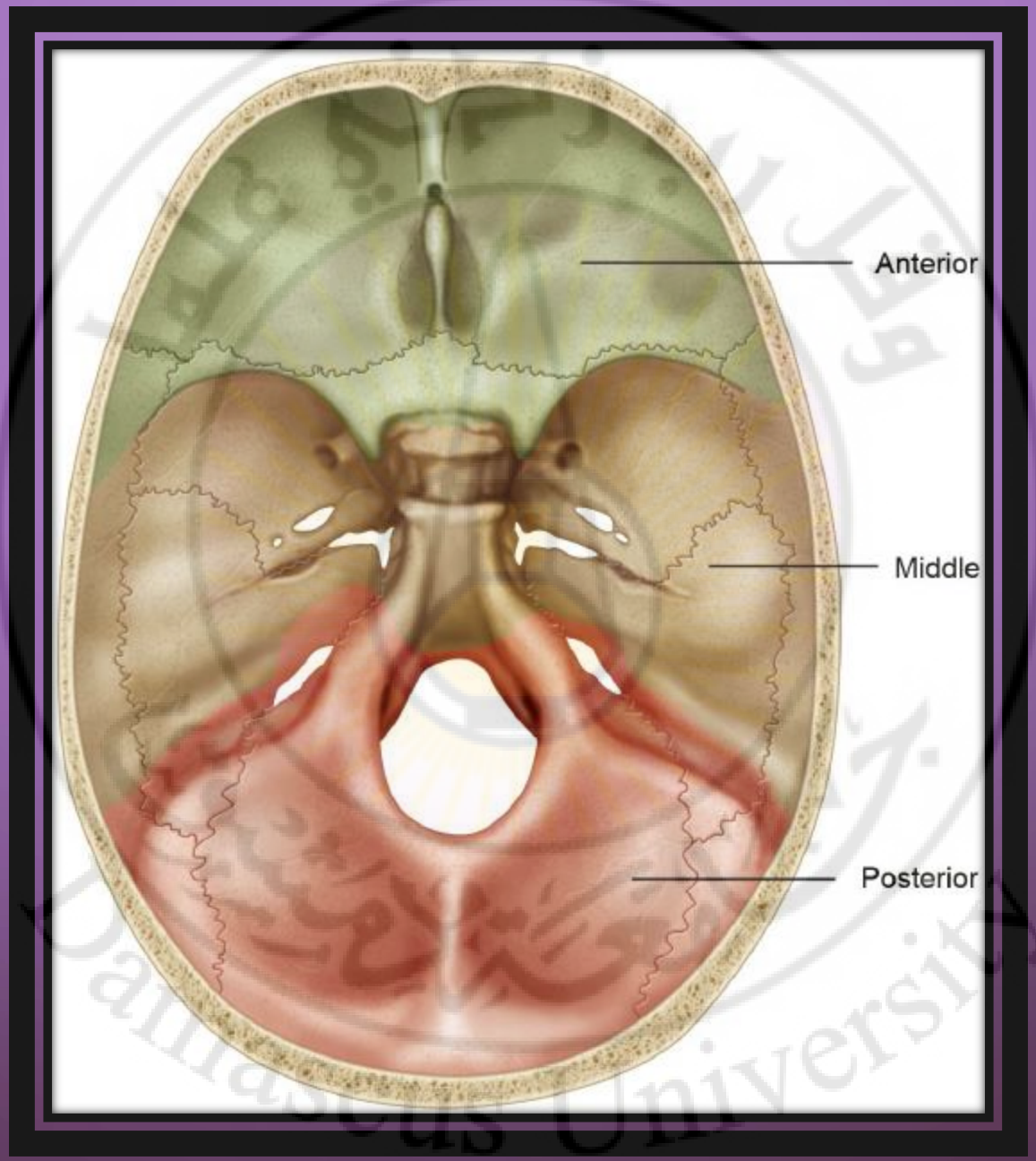
MD MRCP(LONDON) FRCP(EDIN)

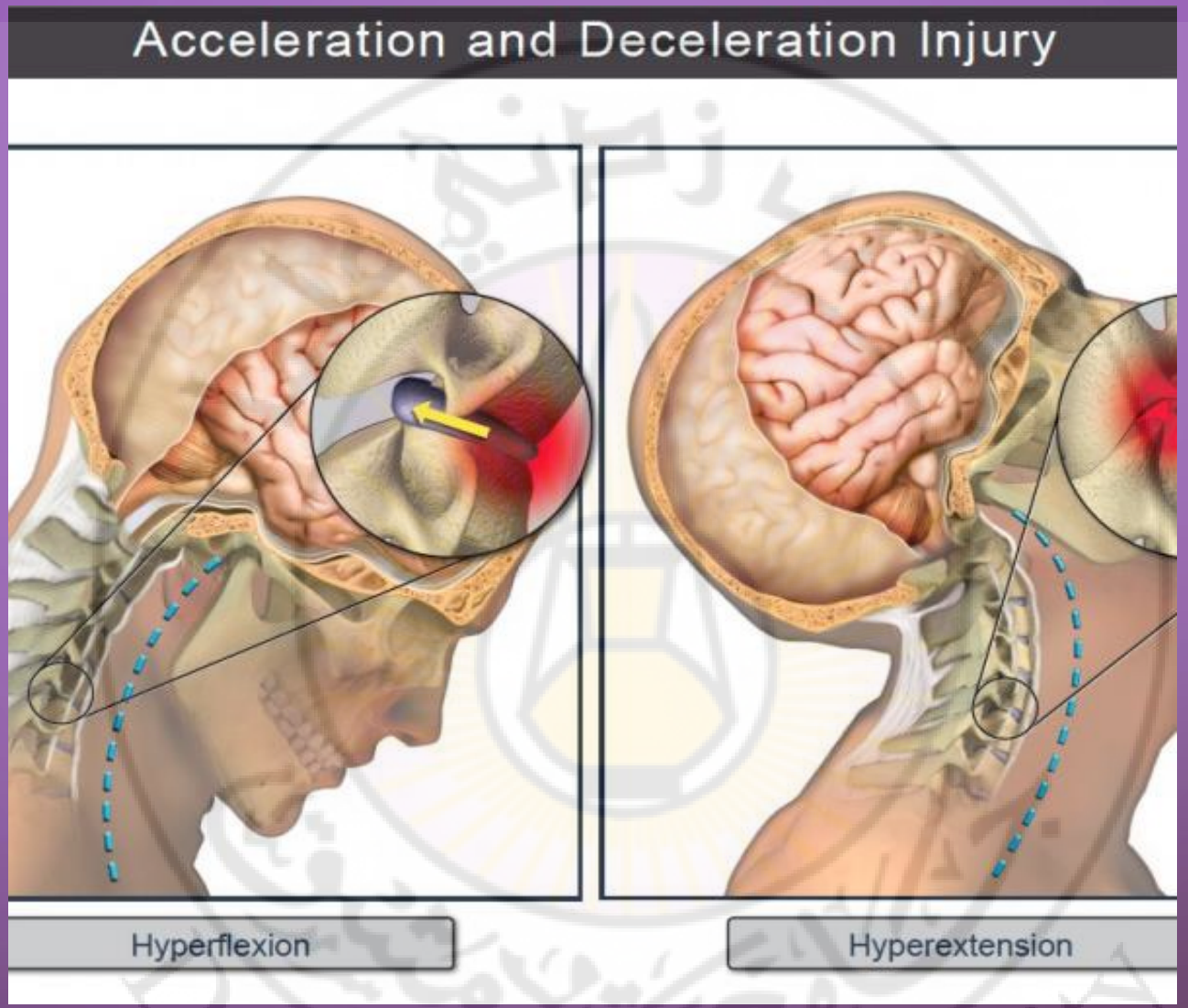


Causes of Brain Injury

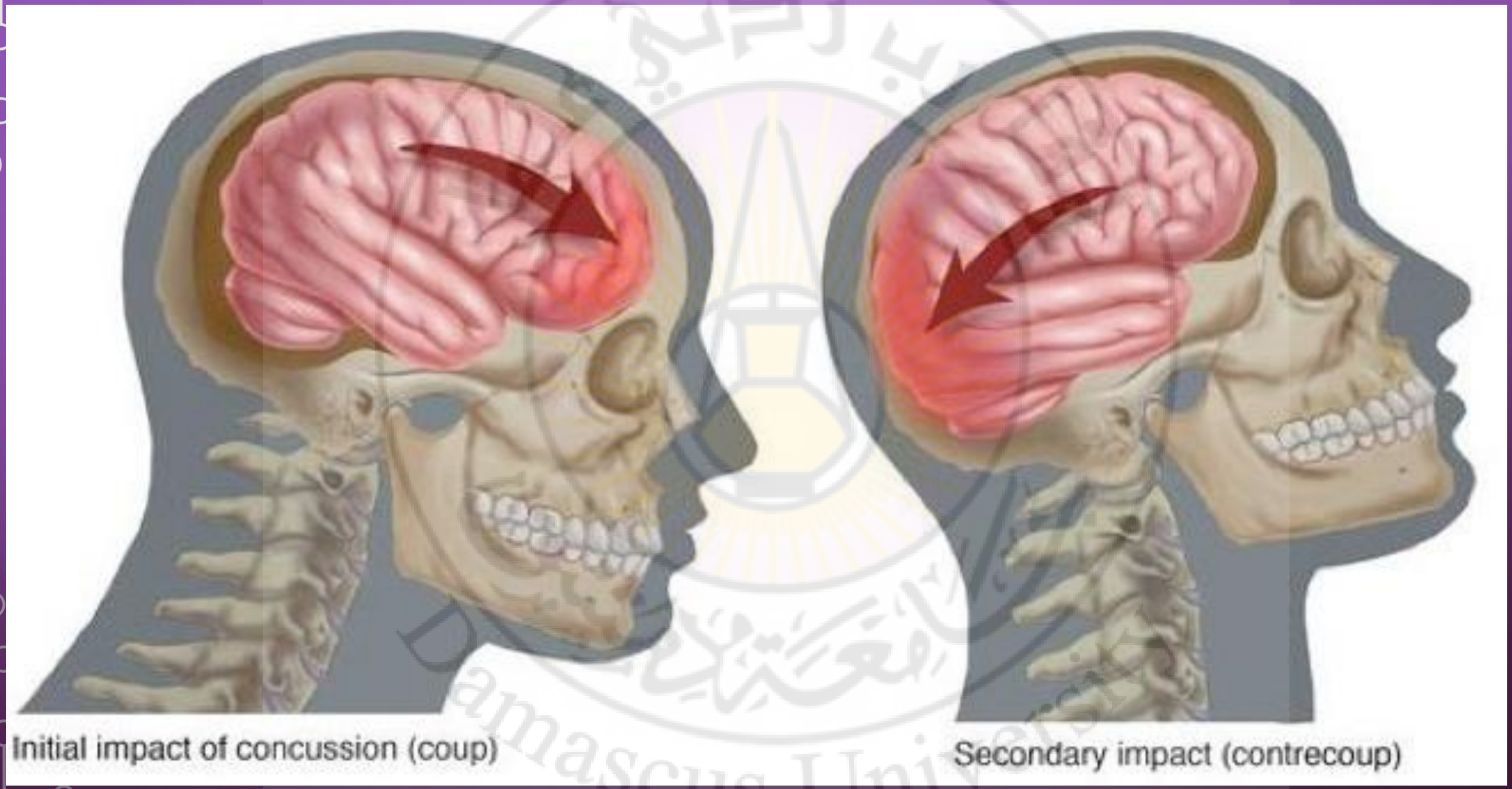


The brain is an organ of relatively soft consistency contained in a rigid, compartmentalized, unyielding box which has a rough and irregular bottom

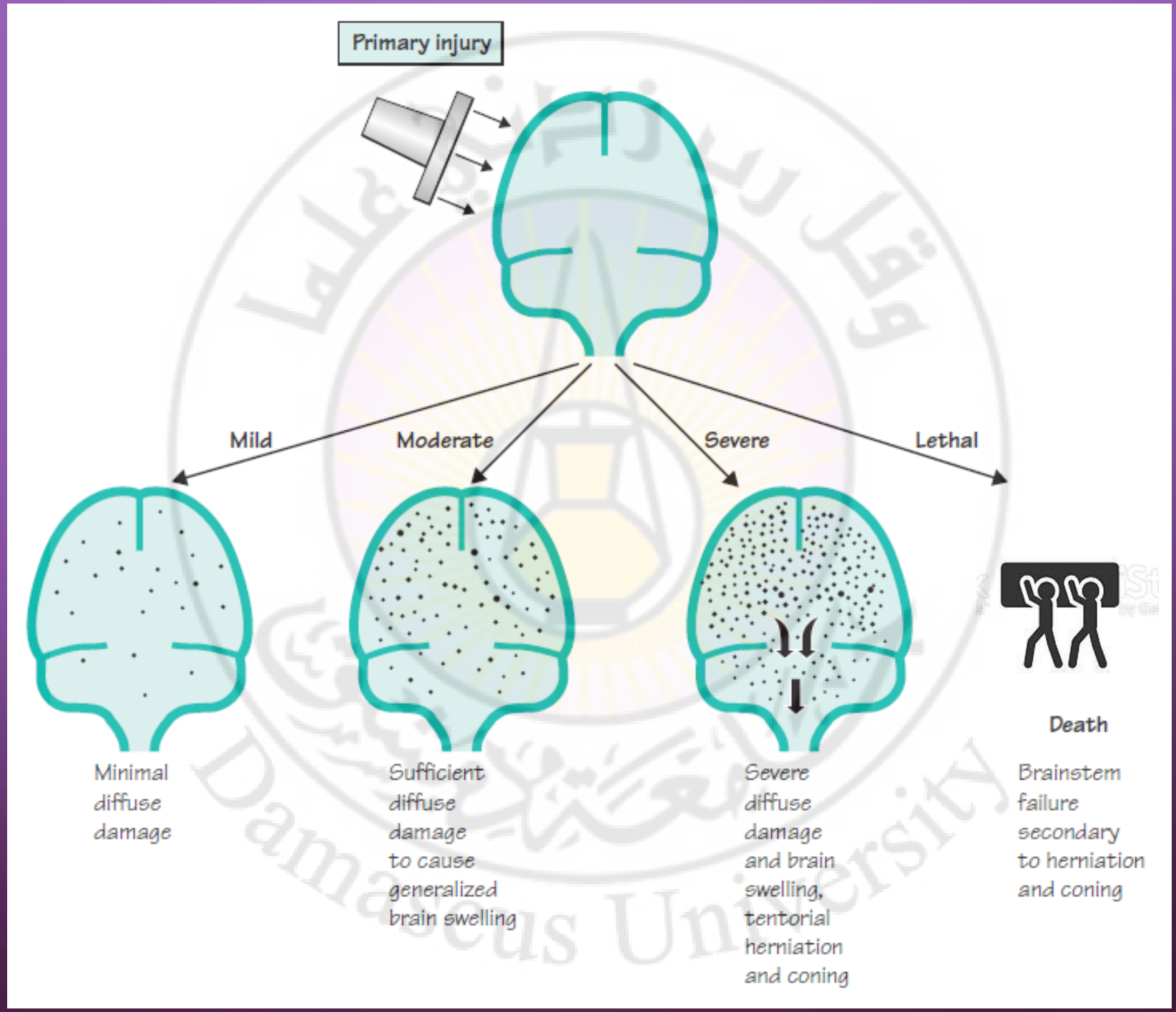

Anterior
Middle
Posterior

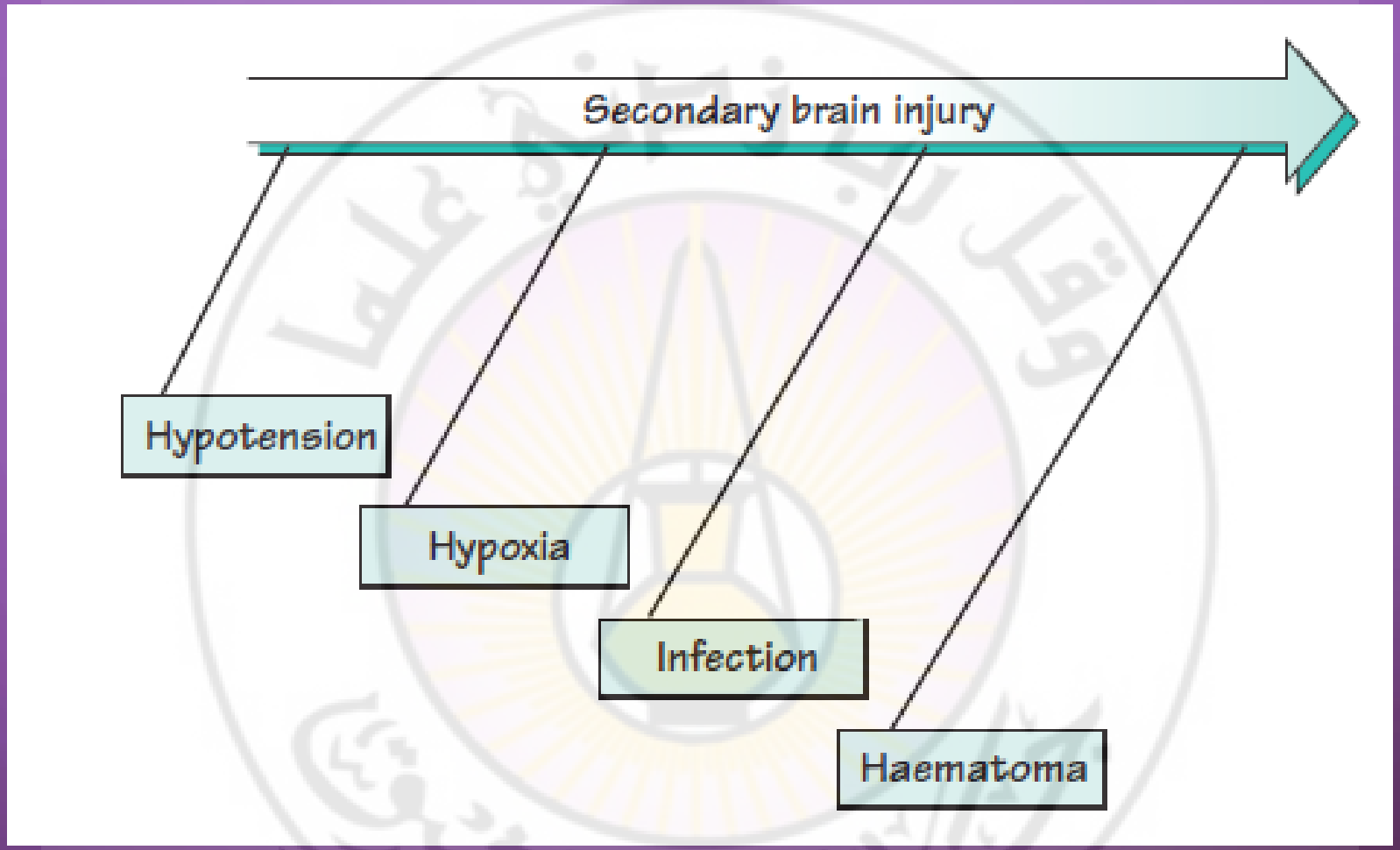


Acceleration (increasing speed)
deceleration (decreasing speed)


Initial impact of concussion (coup)
Secondary impact (contrecoup)

The most common injury resulting from car accidents is whiplash, which accounts for **80% of all car crash injuries**. Whiplash is considered an acceleration-deceleration injury, which can also include shoulder injuries and traumatic brain injuries.


Primary injury
Mild
Moderate
Severe
Lethal
Minimal diffuse damage
Sufficient diffuse damage to cause generalized brain swelling
Severe diffuse damage and brain swelling, tentorial herniation and coning
Death
Brainstem failure secondary to herniation and coning



The four main additional insults, any of which may produce further brain swelling, and push the patient in the direction of secondary brainstem damage and death

Secondary brain injury

The four additional insults will show their adverse influence on the brain by :

- declining performance in Glasgow Coma Scale observations
- an epileptic fit
- impaired brainstem function observations

Hypotension

Clinical clues

- Large scalp laceration i.e. external blood loss
- Associated major injury to chest, abdomen, pelvis, limbs, i.e. external and internal blood loss
- History that the patient was propped upright after injury with known blood loss and probable hypotension

Hypoxia

- Patient found face down, unconscious
- Upper airways obstruction whilst unconscious
- Severe associated facial injury
- Aspiration of blood or vomit into trachea
- Prolonged epileptic fit
- Associated injury to chest wall or lungs
- Respiratory depression by alcohol or drugs

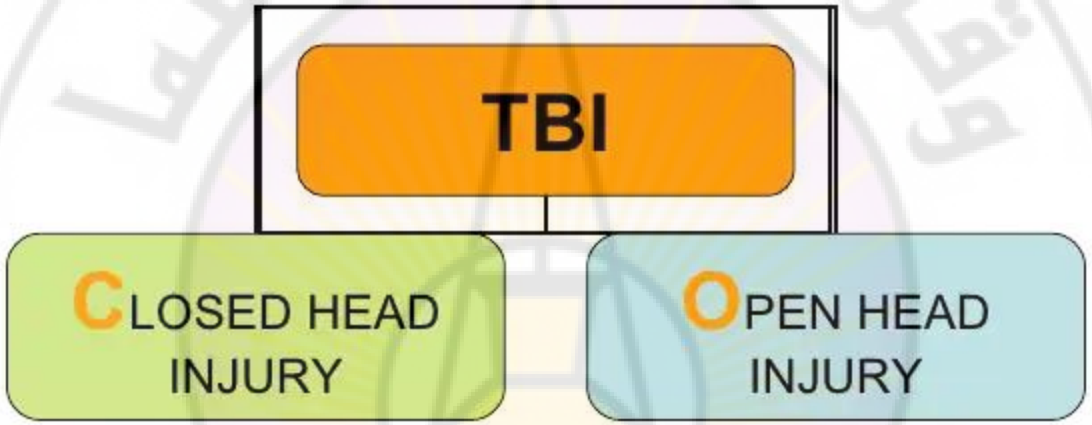
Infection

- Open scalp wound over skull fracture
- Leakage of CSF from scalp wound, nose or ear
- Inadequate inspection, cleaning, or debridement of open scalp wound over fracture site
- Skull fracture found on CT scan in region of wound, nose or ear
- Intracranial air seen on CT scan

Haematoma

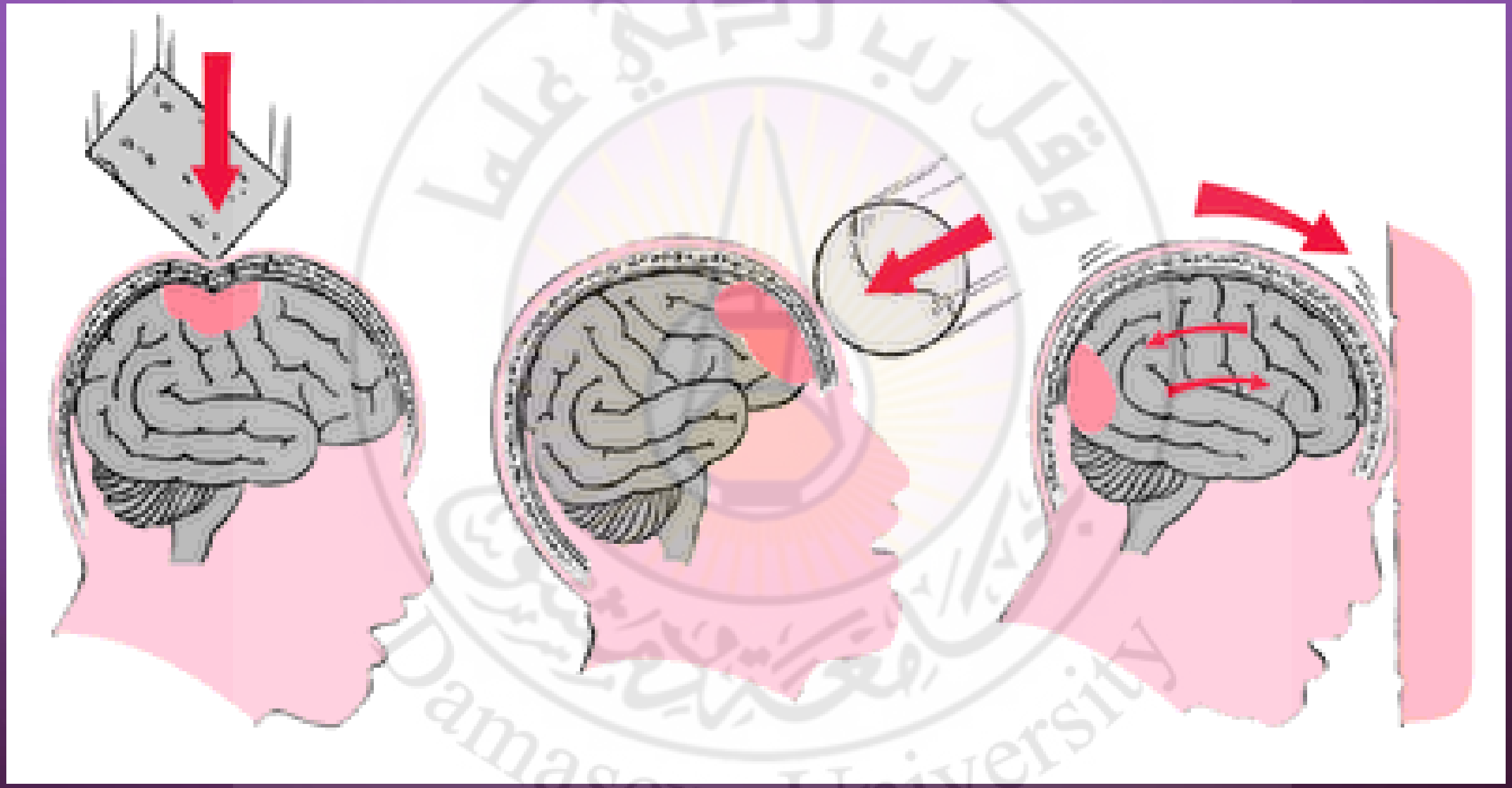
- Factors known to be associated with the development of an intracranial haematoma, whether extradural, subdural or intracerebral :
  - Skull fracture
  - Impaired conscious level (even disorientation) i.e. a fully orientated patient with no skull fracture is very unlikely to develop a haematoma

Hypotension	Hypoxia	Infection	Haematoma
Clinical evidence			
• Development of shock Low blood pressure Rapid pulse Sweating	• Noisy obstructed breathing • Abnormal chest movement • Abnormal respiratory rate • Abnormal chest X-ray • Abnormal blood gases	• Purulent discharge from scalp wound • Proved infection of CSF	• CT scan



No obvious external signs, resulting from –motor vehicle crashes, falls, child abuse, or domestic violence, child violence..

Obvious external wound For example a gunshot wound or object penetrating the skull.



CLASSIFICATION

- **SCALP INJURY:**

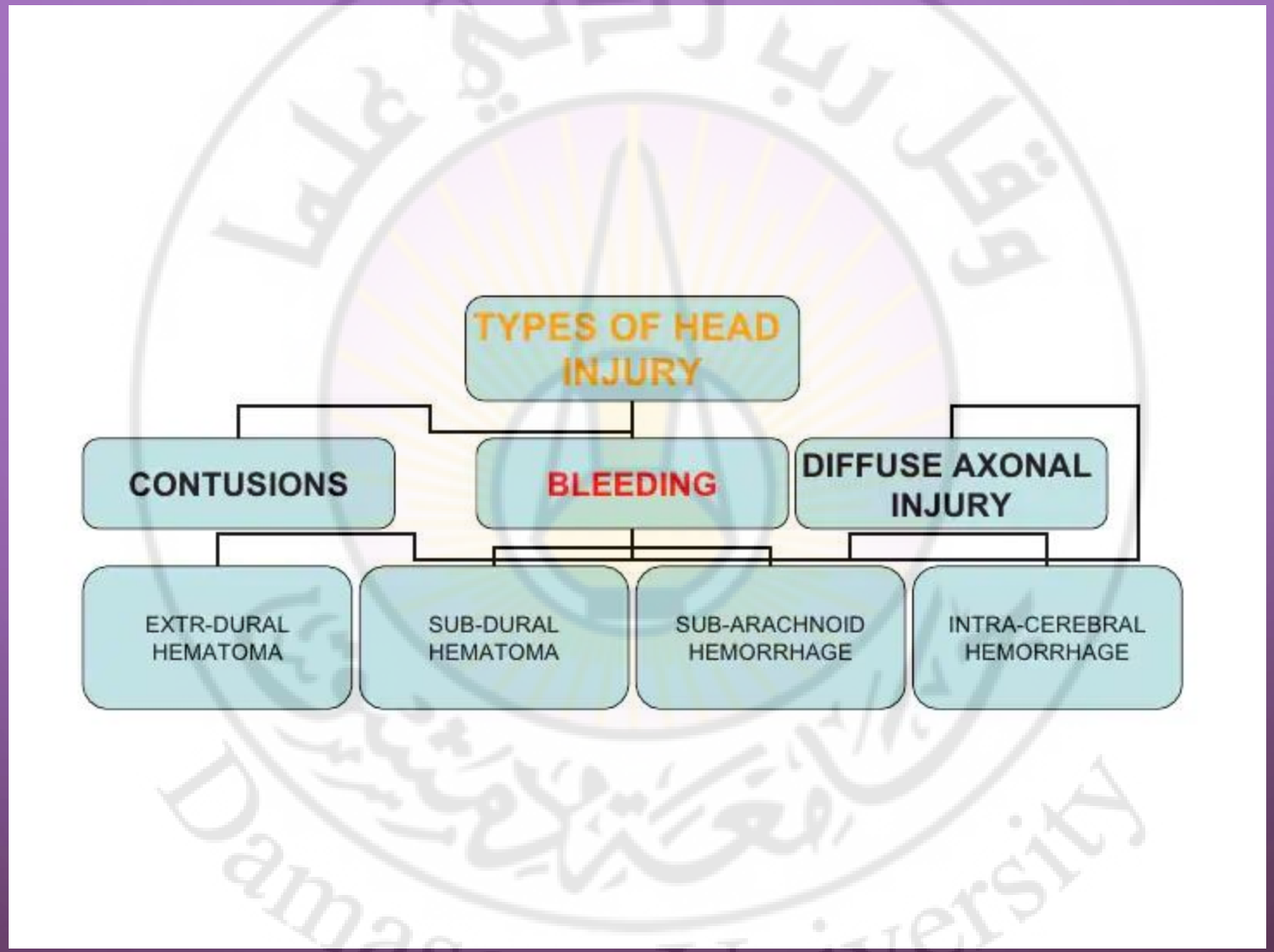
  The scalp has many blood vessels, so any scalp injury may bleed profusely. Control bleeding with direct pressure

- **SKULL INJURY:**

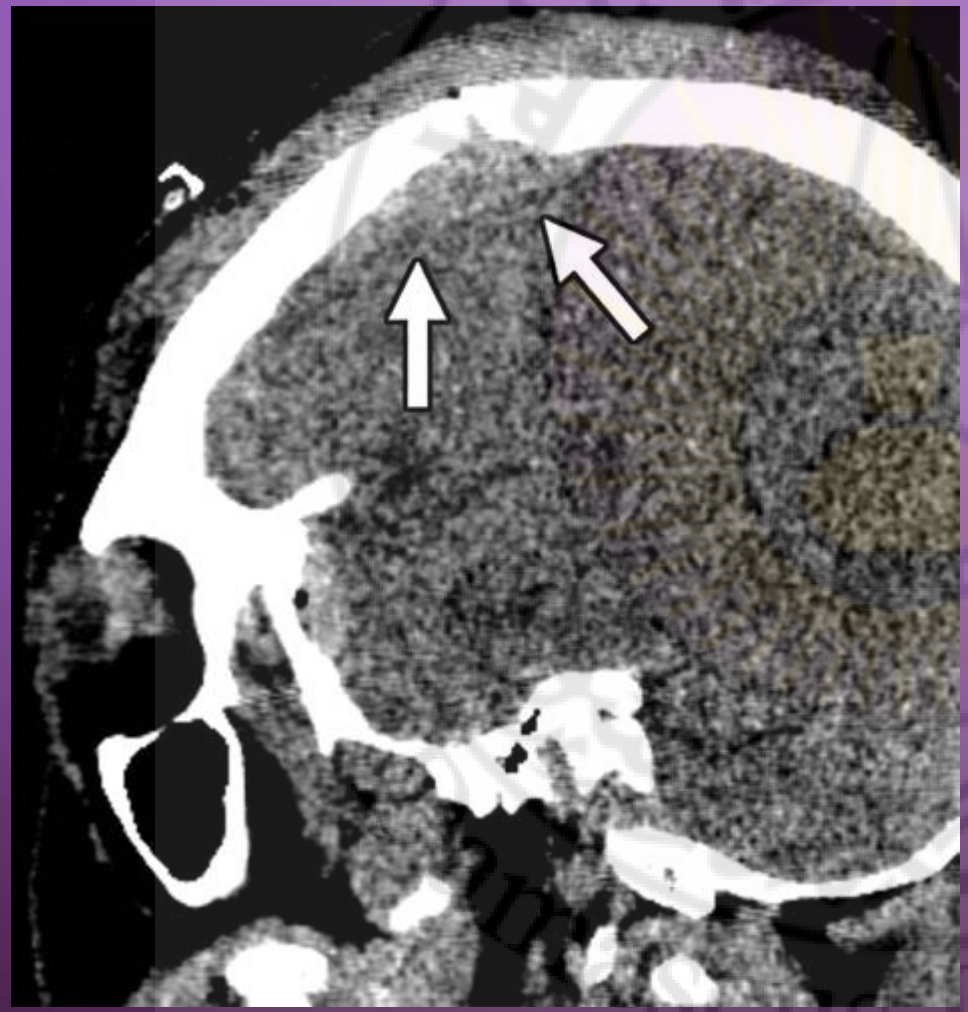
  Skull injury includes fracture to cranium and the face. If severe enough there can be injury to the brain.

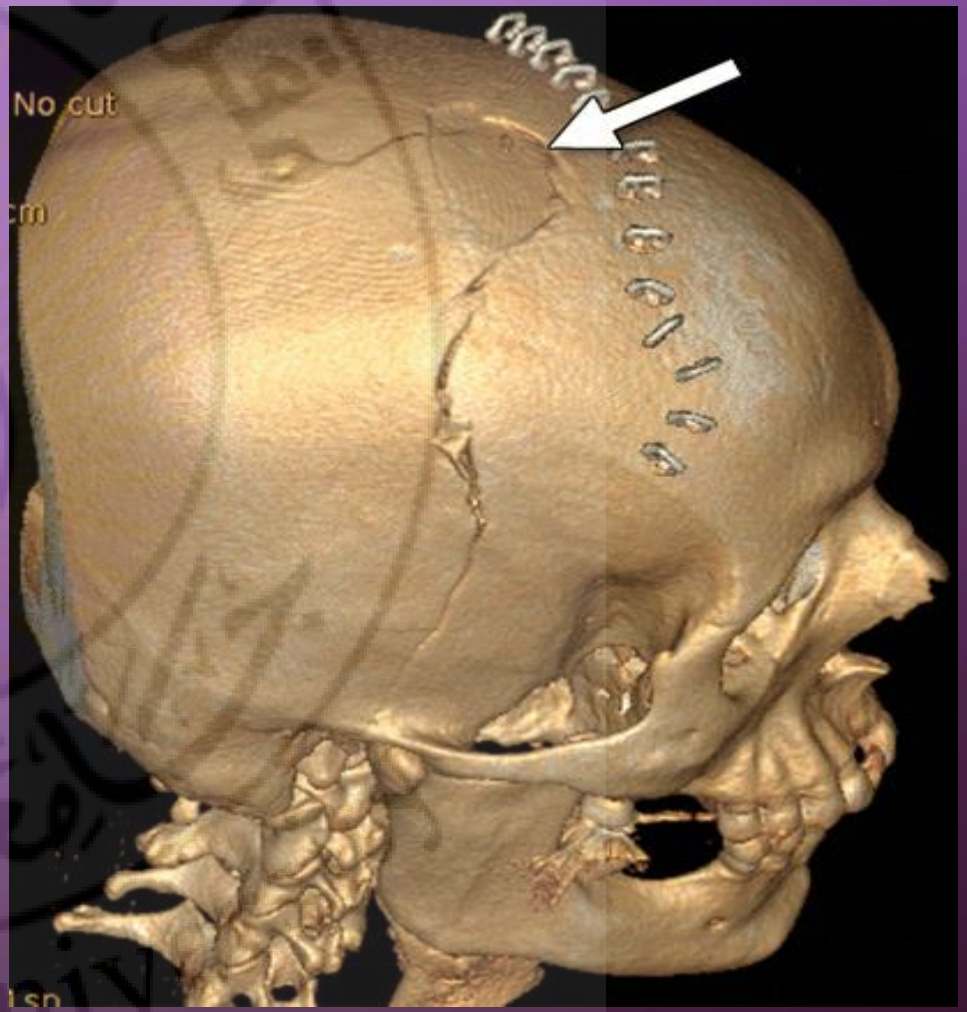
- **BRAIN INJURY:**

  Brain injury can be classified as direct or indirect. Direct injuries to the brain can occur in open head injuries


TYPES OF HEAD INJURY
CONTUSIONS
BLEEDING
DIFFUSE AXONAL INJURY
EXTR-DURAL HEMATOMA
SUB-DURAL HEMATOMA
SUB-ARACHNOID HEMORRHAGE
INTRA-CEREBRAL HEMORRHAGE

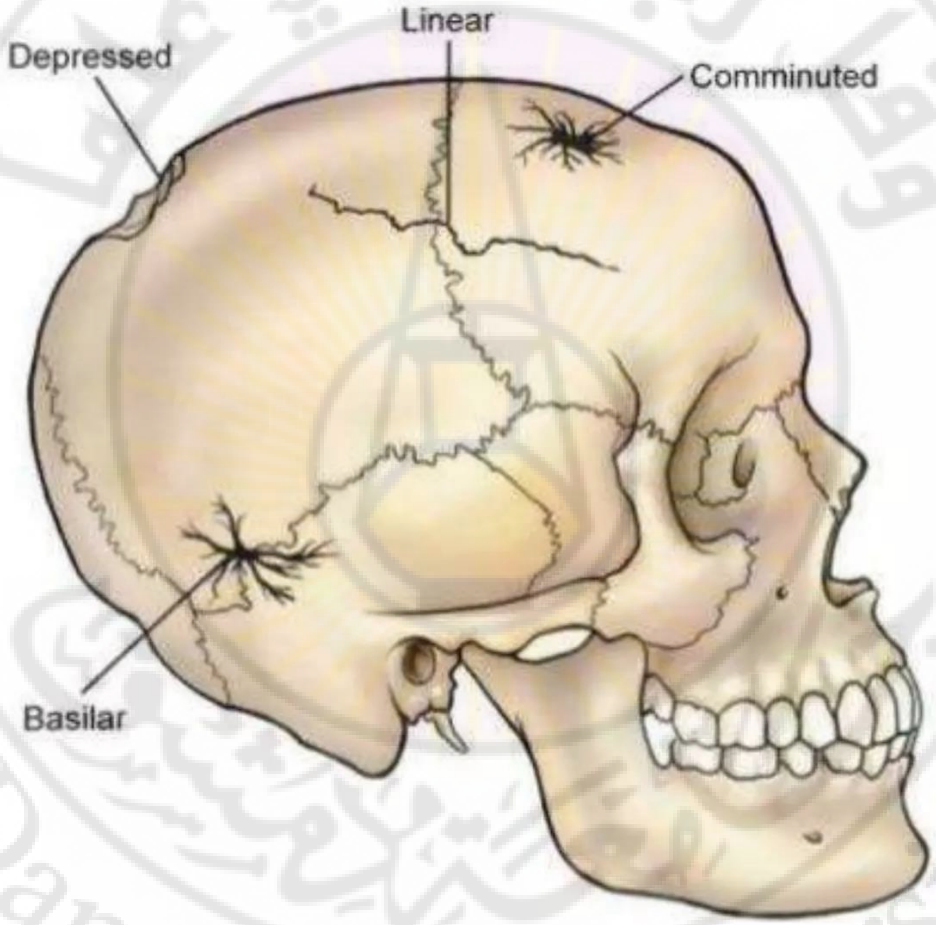
Focal depressed skull fracture in a young man who was hit on the head by a falling brick. Three-dimensional (3D) reconstructed (left) show a focally depressed comminuted skull fracture (arrows). Sagittal CT image (right) shows an associated underlying small lentiform EDH (arrows). There was no hemorrhagic contusion or SAH.

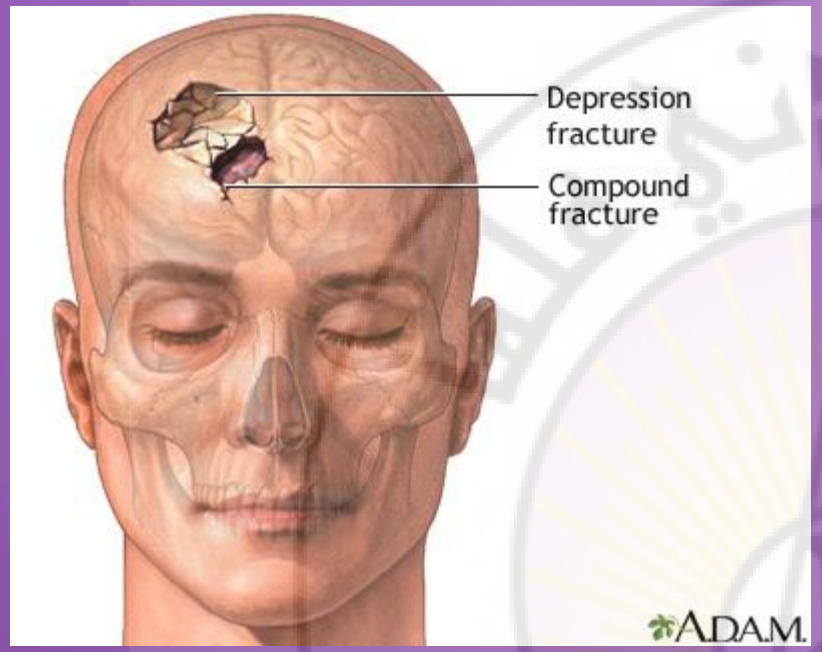


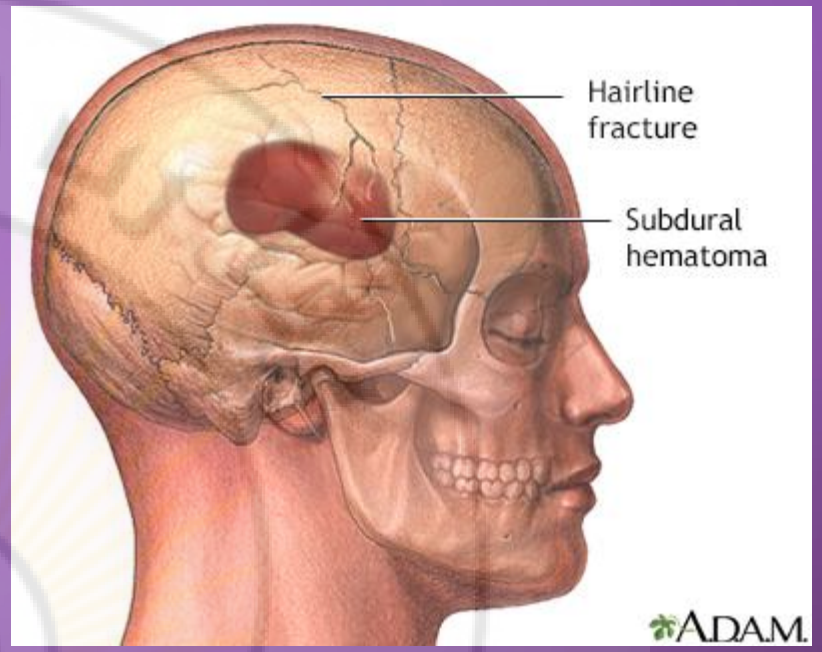


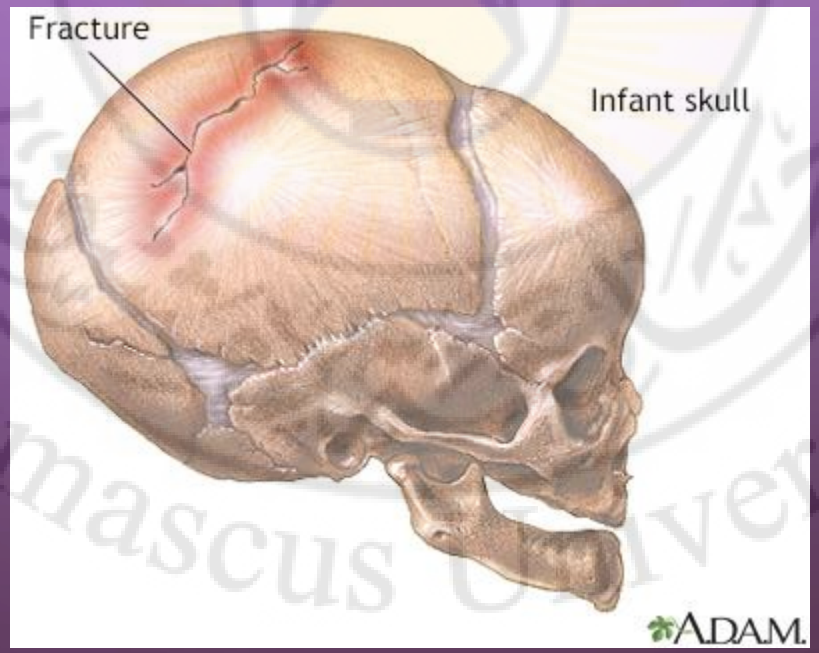

LACERATIONS
Secure ABC
Expose, clean, apply pressure dressing if bleeding

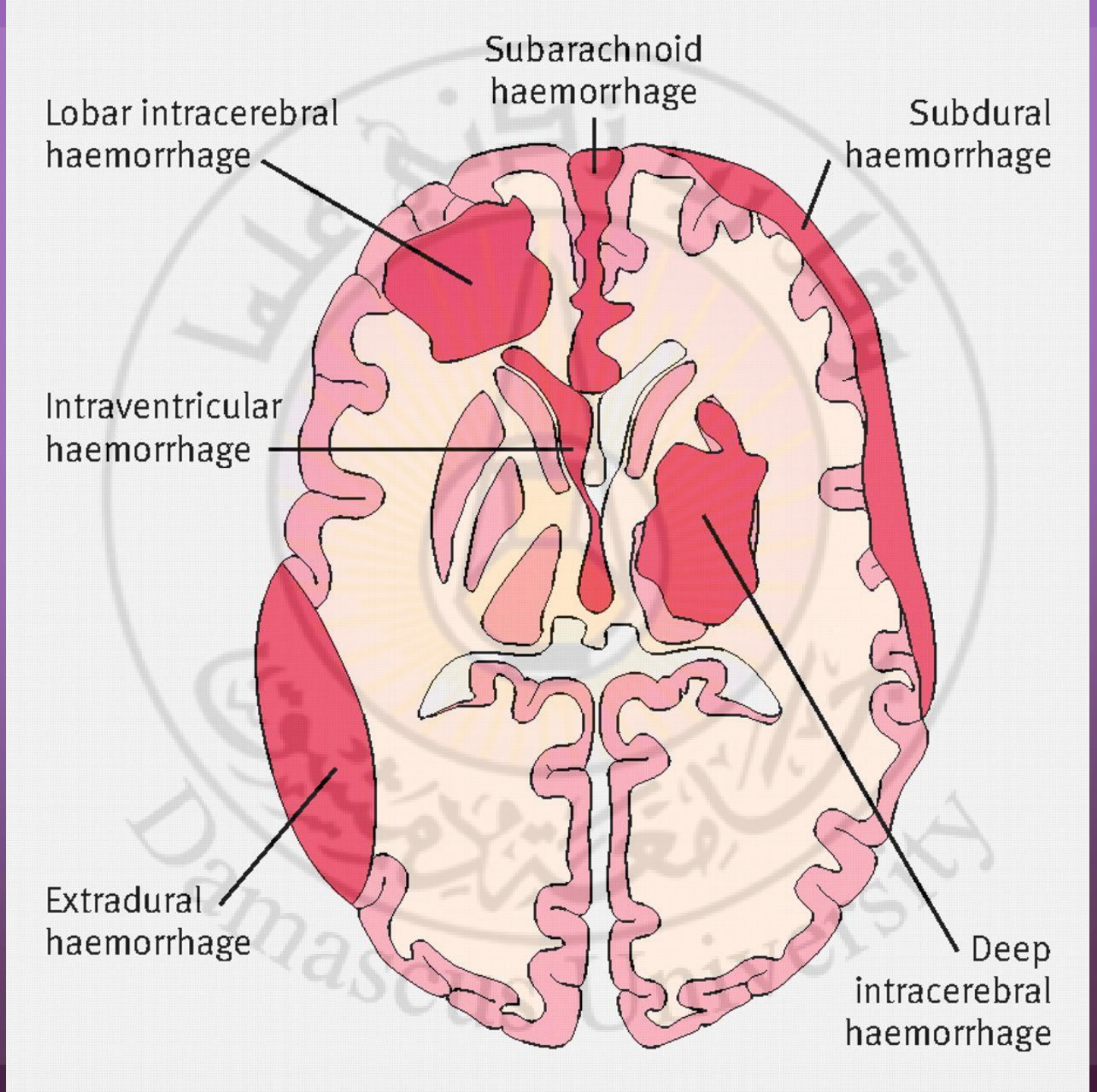

CONCUSSION
When the brain suddenly shifts inside the skull and knocks against the skulls bony surface. Concussions can last from a few moments, to an unconscious state for over 3 minutes.

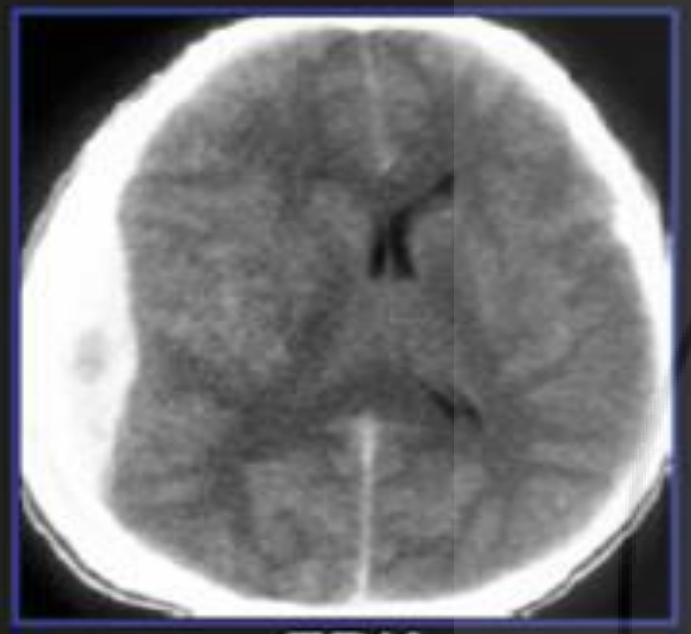

Linear
Depressed
Comminuted
Basilar


Depression fracture
Compound fracture
A.D.A.M.

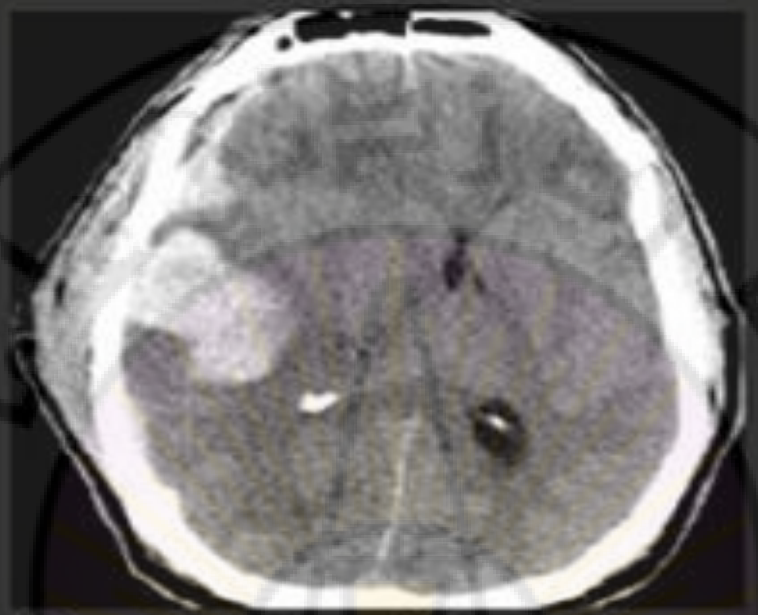

Hairline fracture
Subdural hematoma
A.D.A.M.


Fracture
Infant skull
A.D.A.M.

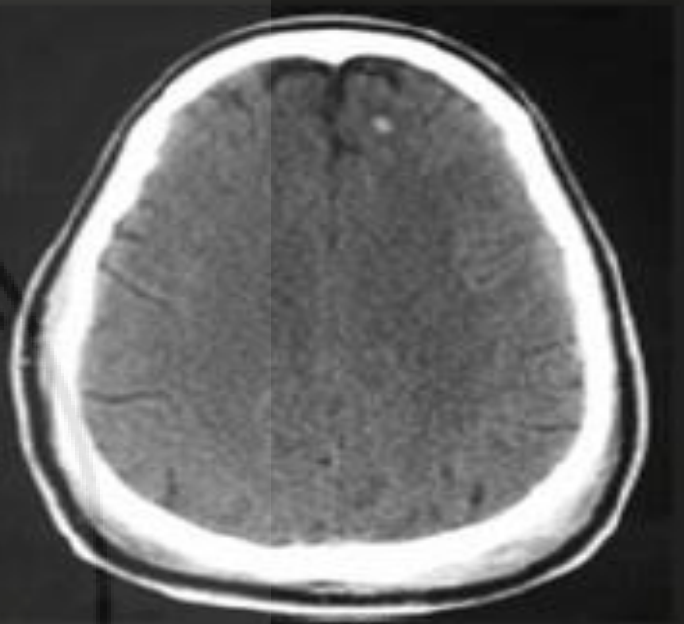

Subarachnoid haemorrhage
Lobar intracerebral haemorrhage
Subdural haemorrhage
Intraventricular haemorrhage
Extradural haemorrhage
Deep intracerebral haemorrhage



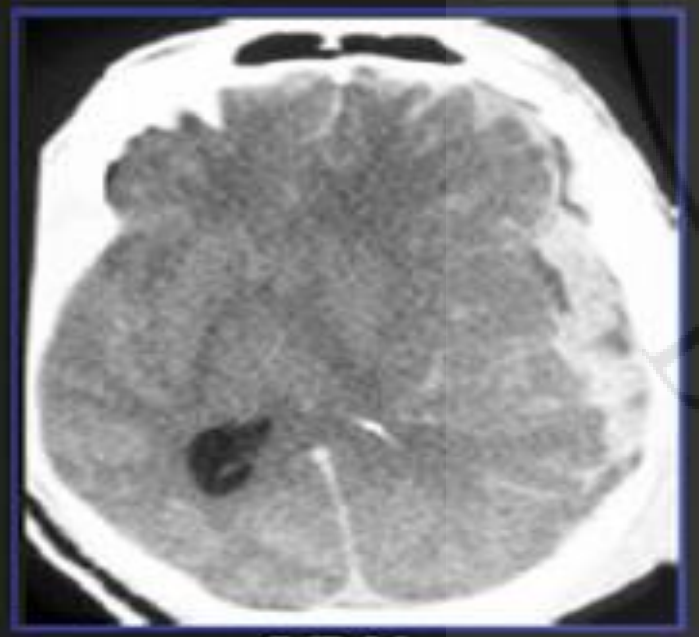
EDH



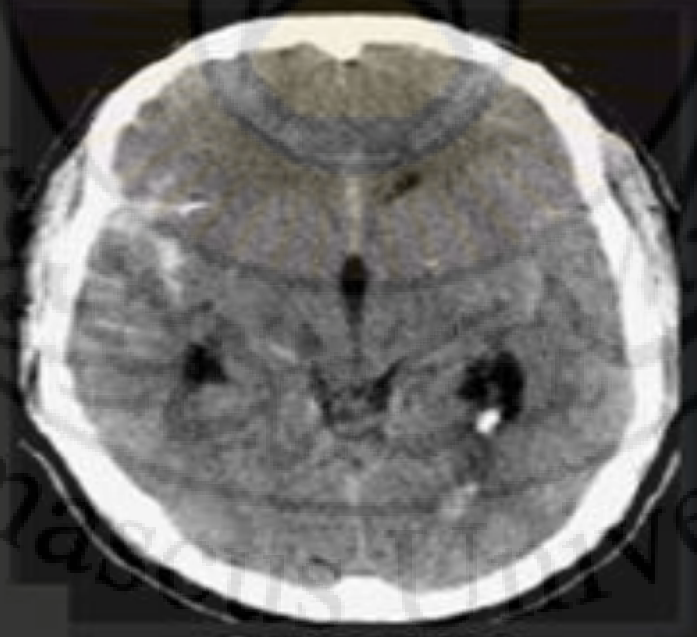
Contusion/Hematoma



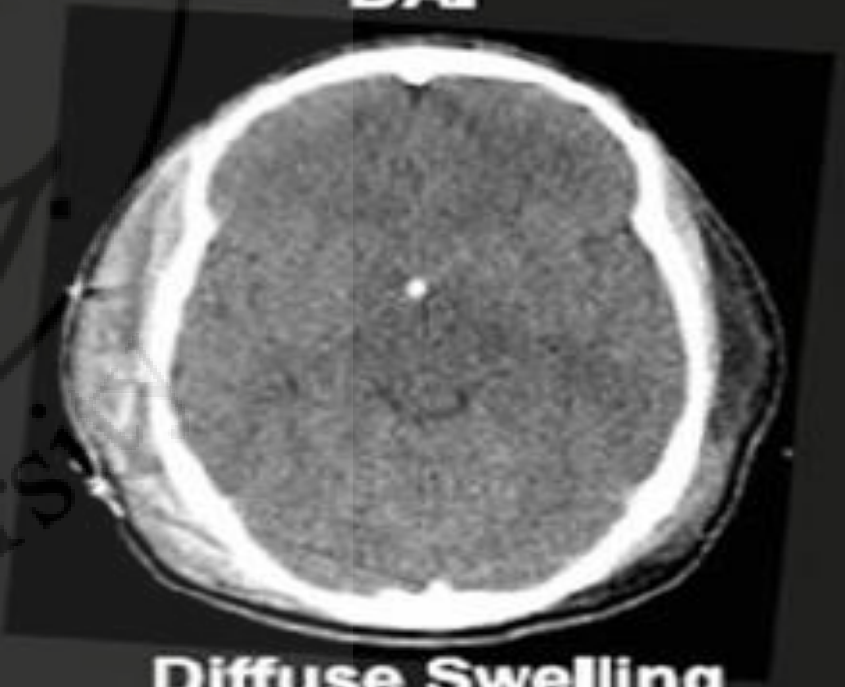
DAI



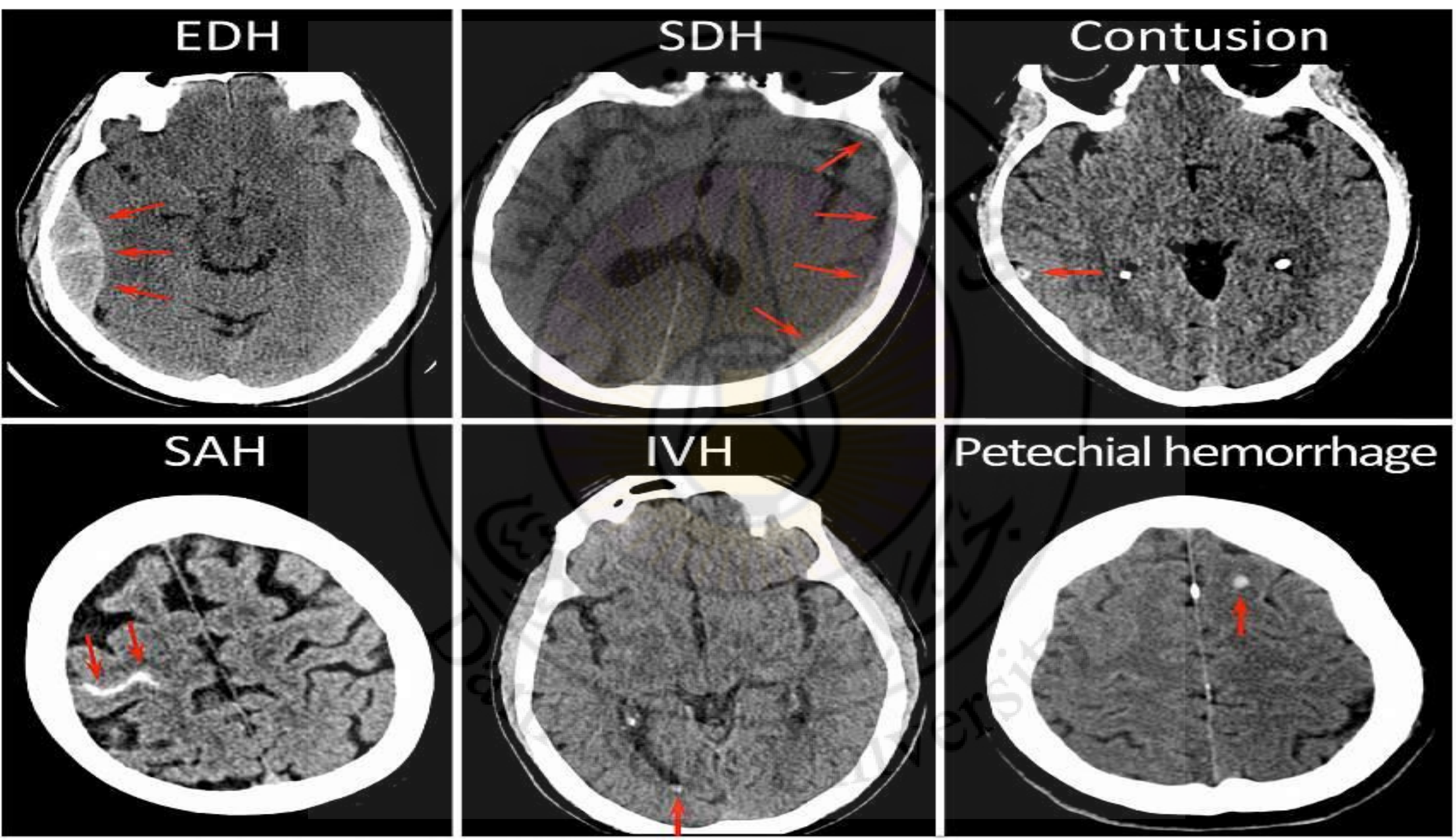
SDH



SAH/IVH



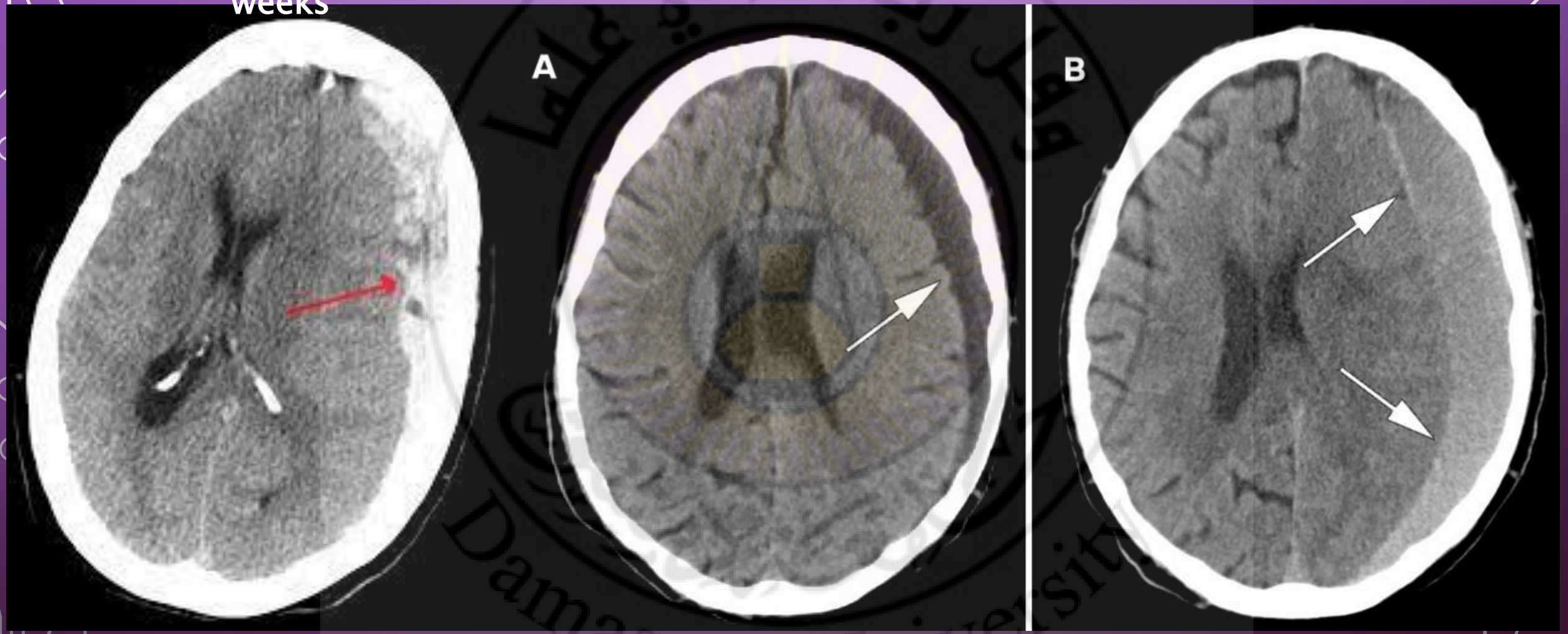
Diffuse Swelling

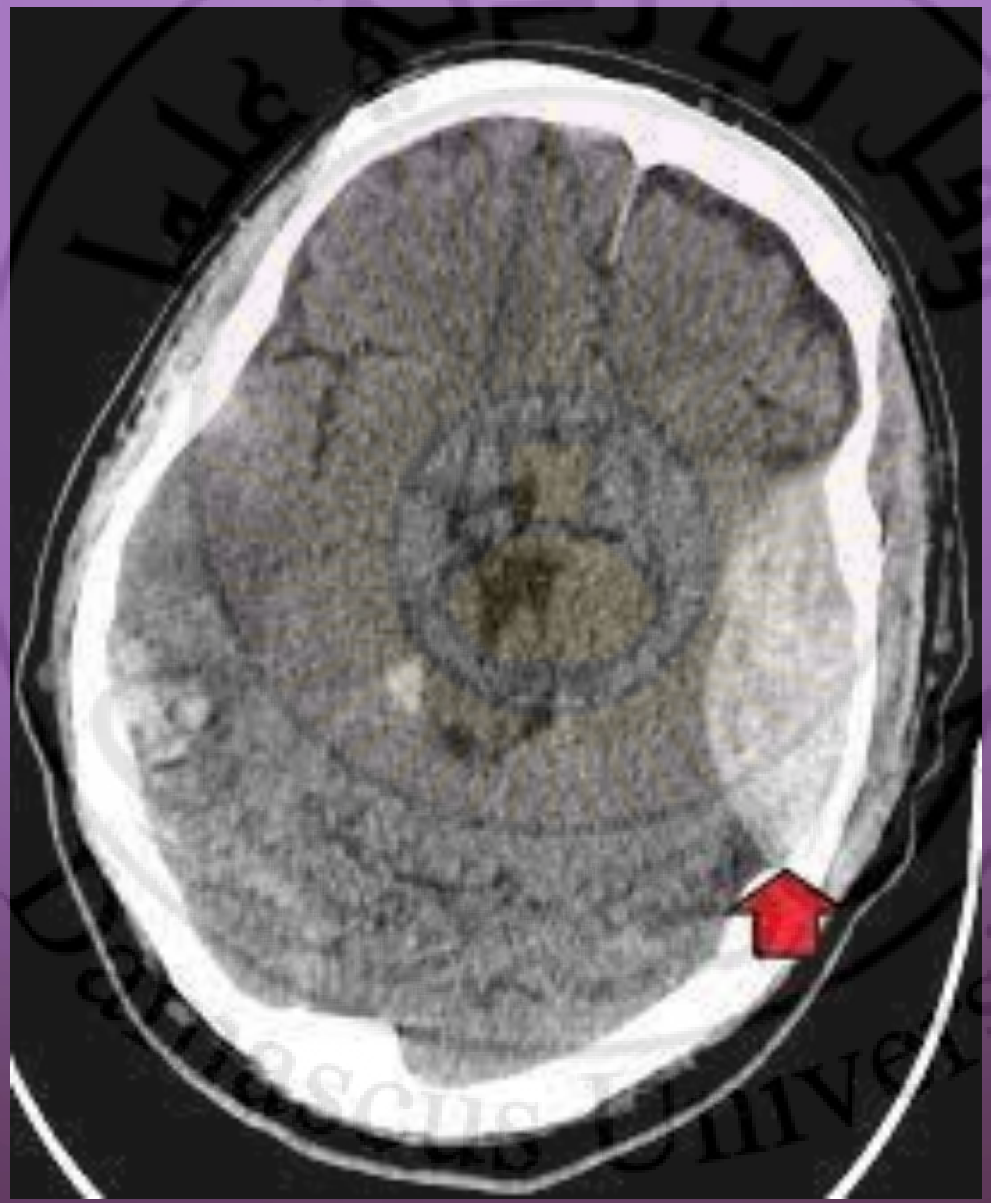

EDH
SDH
Contusion
SAH
IVH
Petechial hemorrhage

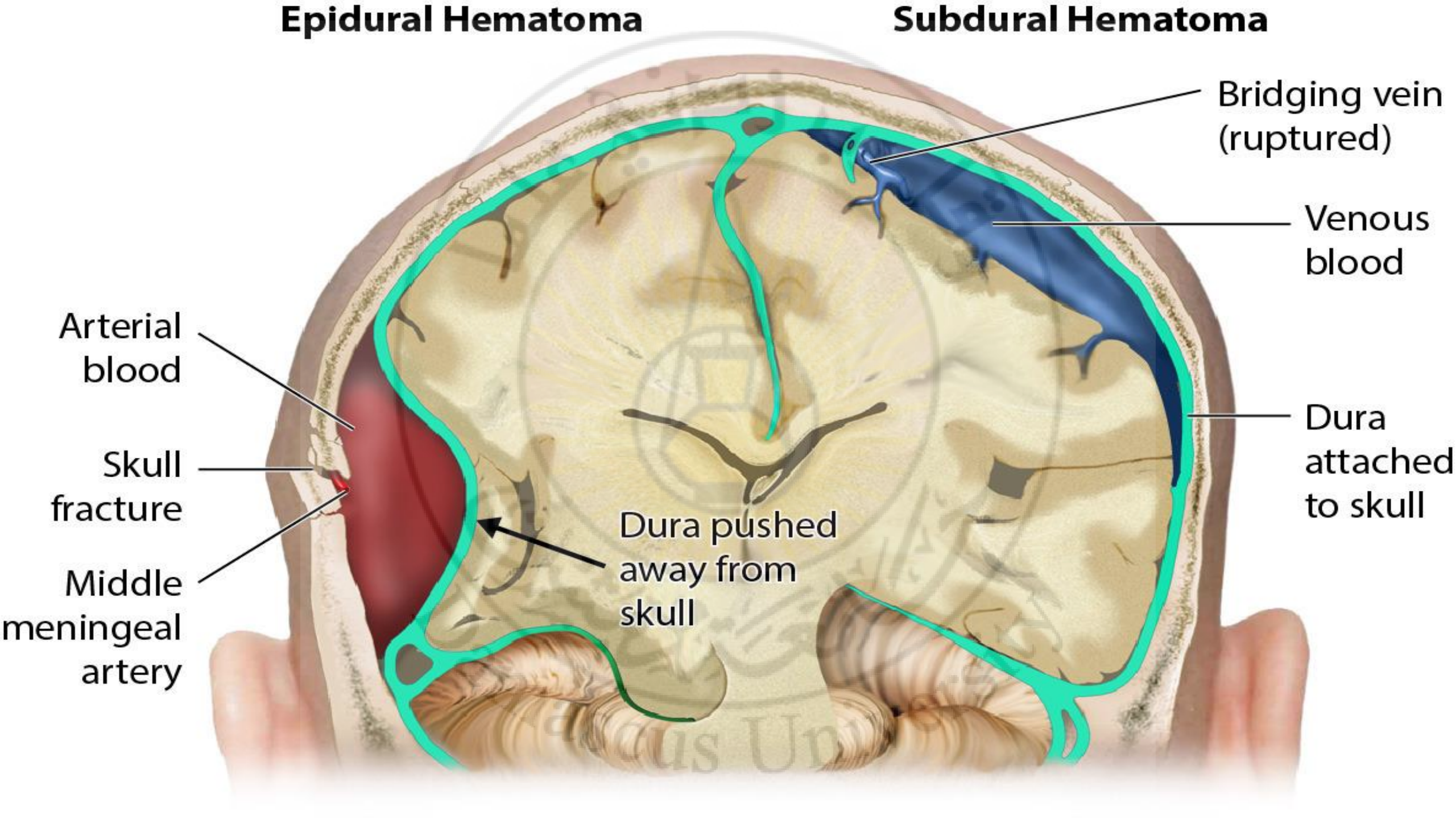
Up to 2 weeks

> 4 weeks

2 – 4 weeks

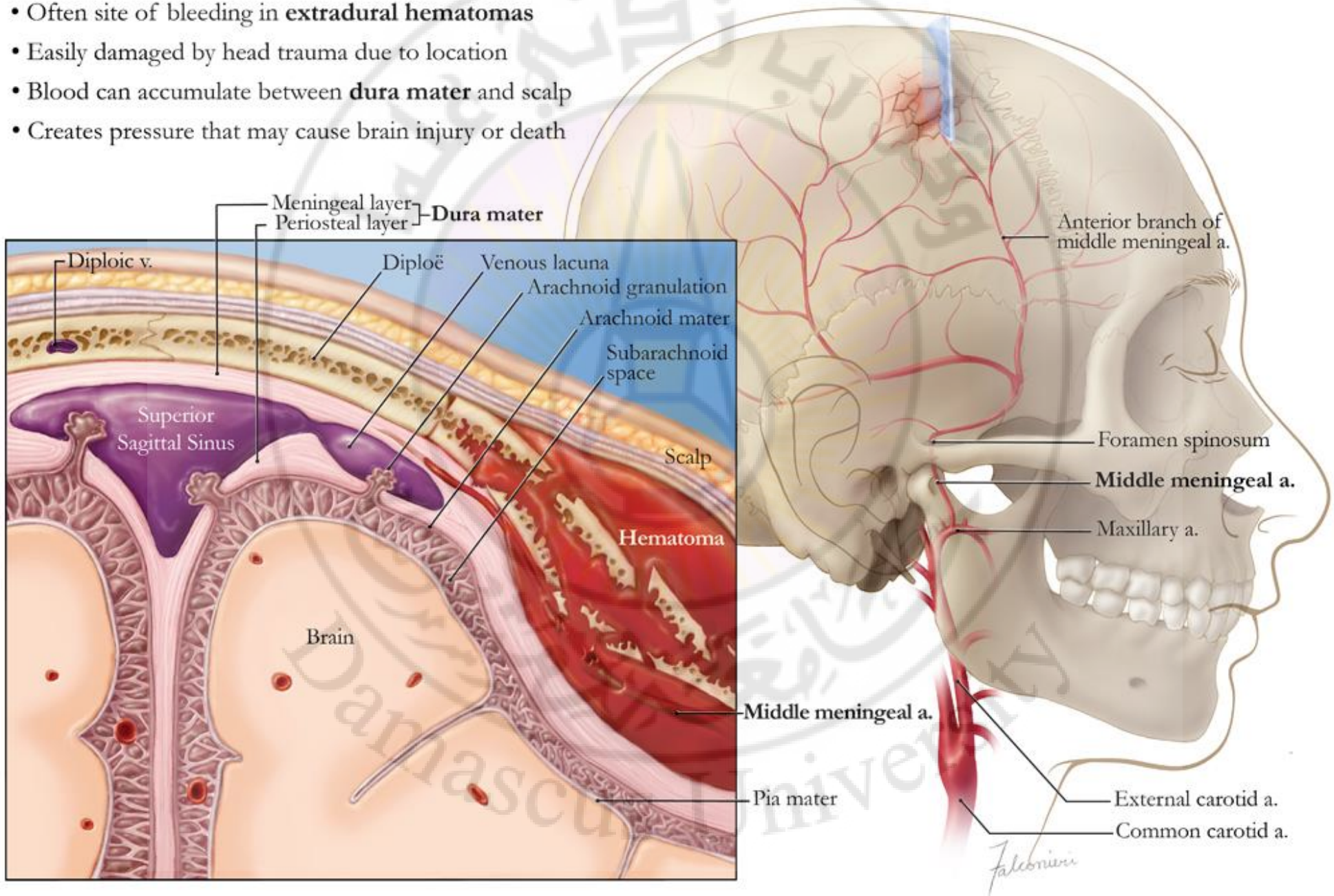


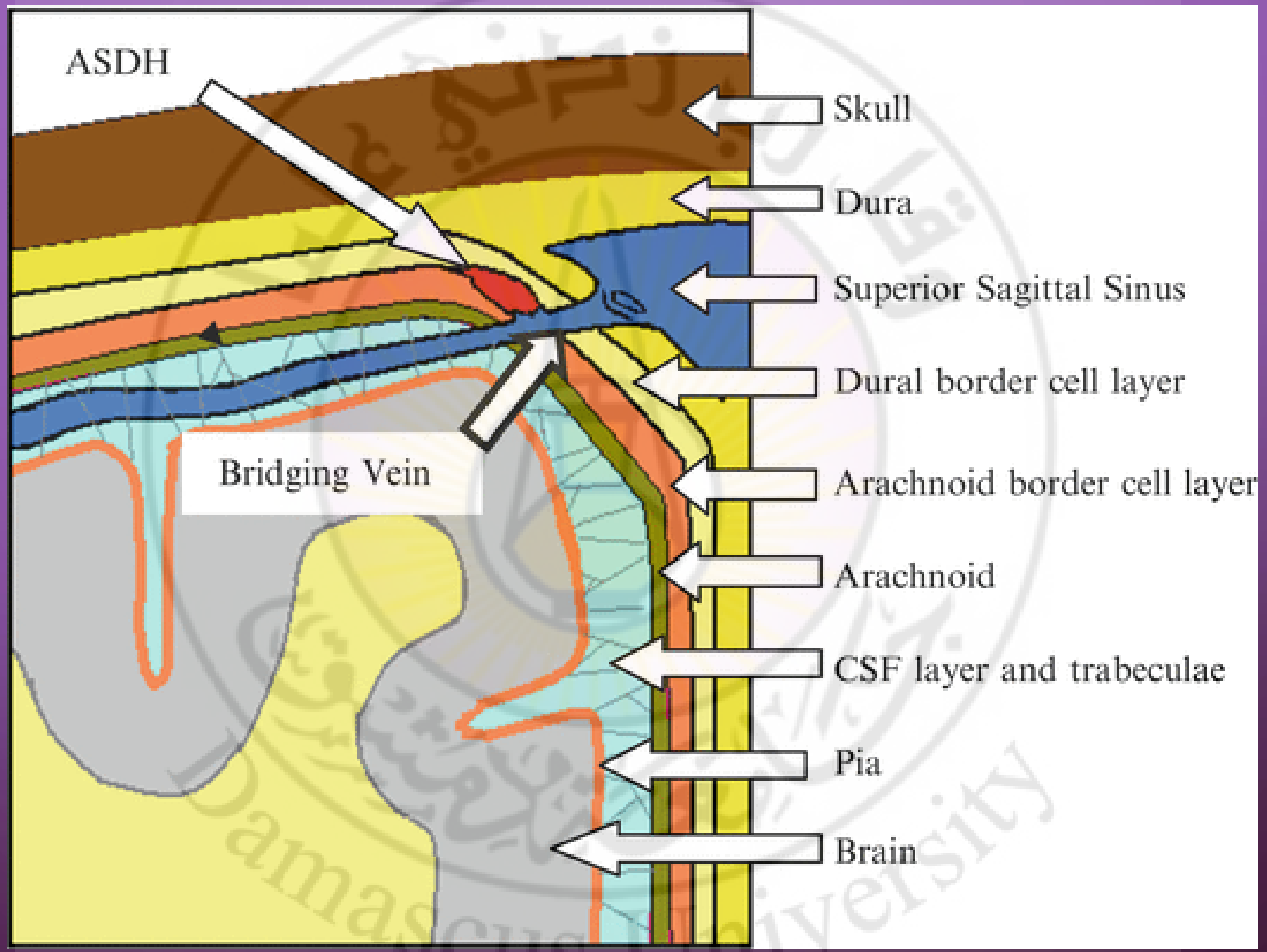


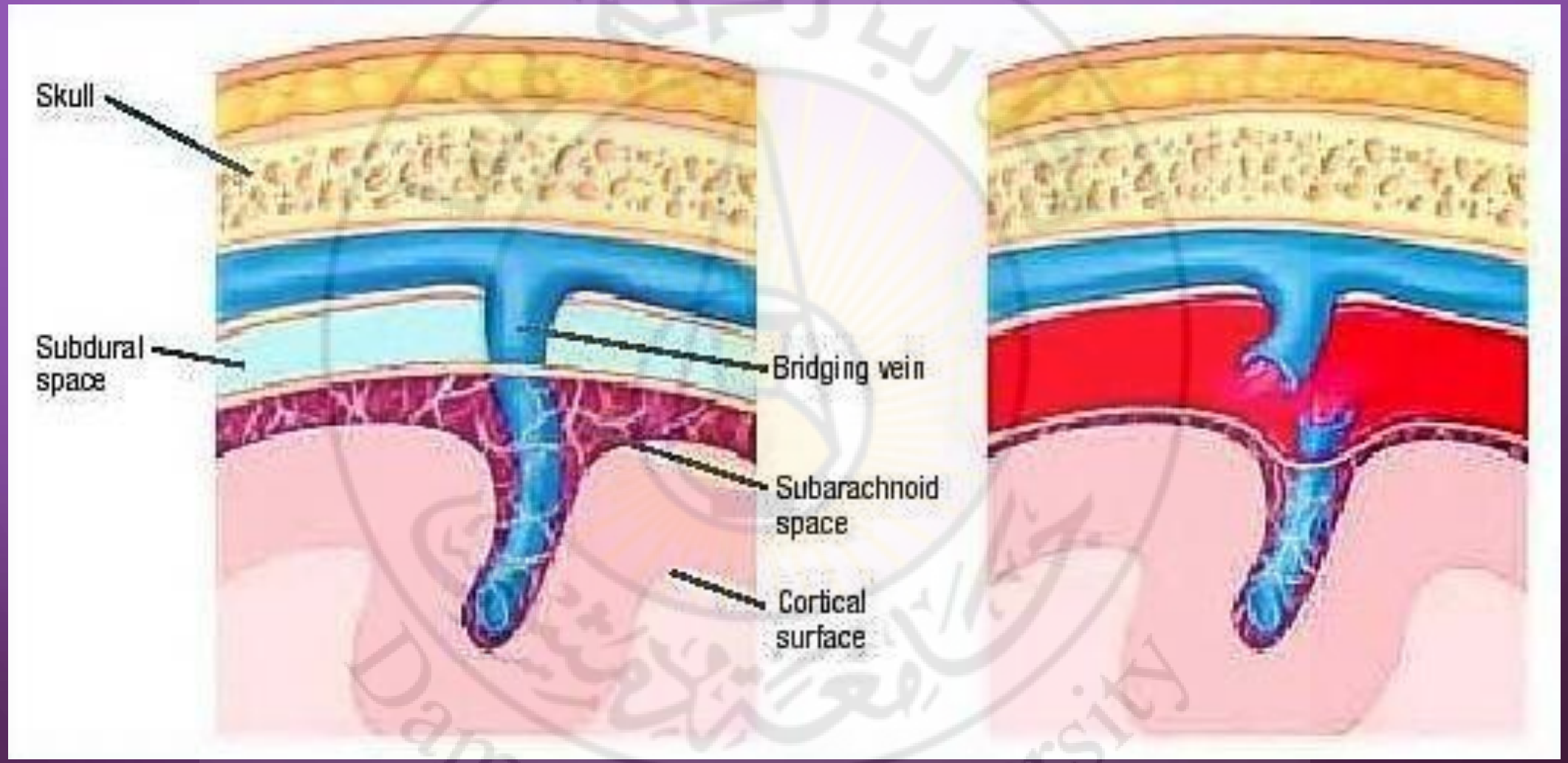

Epidural Hematoma
Subdural Hematoma
Bridging vein (ruptured)
Venous blood
Arterial blood
Skull fracture
Middle meningeal artery
Dura pushed away from skull
Dura attached to skull

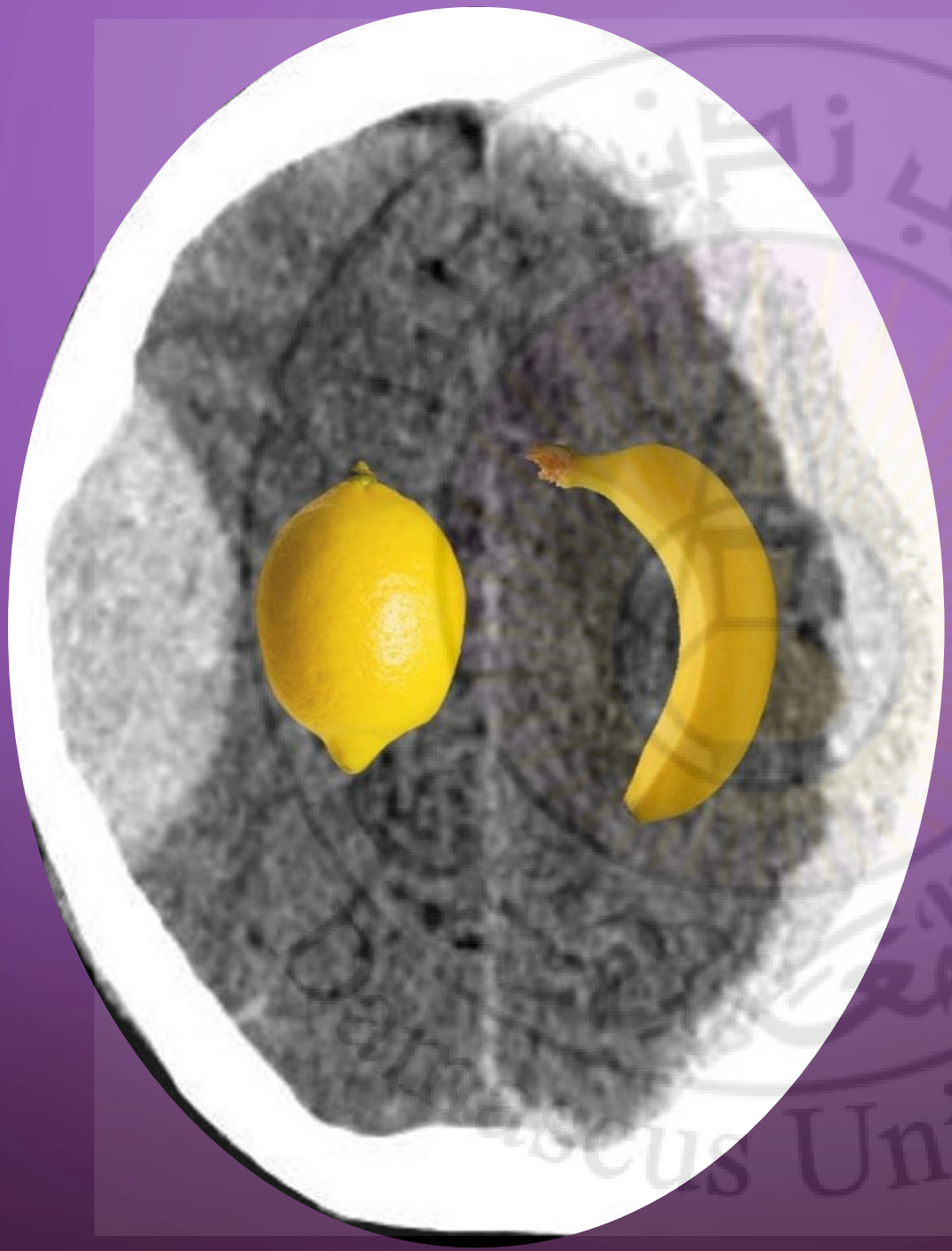
Middle Meningeal Artery in Extradural Hematoma

- Often site of bleeding in **extradural hematomas**
- Easily damaged by head trauma due to location
- Blood can accumulate between **dura mater** and scalp
- Creates pressure that may cause brain injury or death



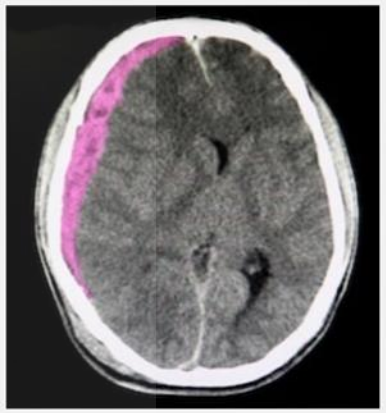

ASDH
Skull
Dura
Superior Sagittal Sinus
Dural border cell layer
Bridging Vein
Arachnoid border cell layer
Arachnoid
CSF layer and trabeculae
Pia
Brain


Skull
Subdural space
Bridging vein
Subarachnoid space
Cortical surface

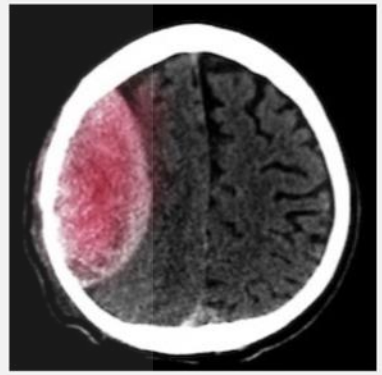


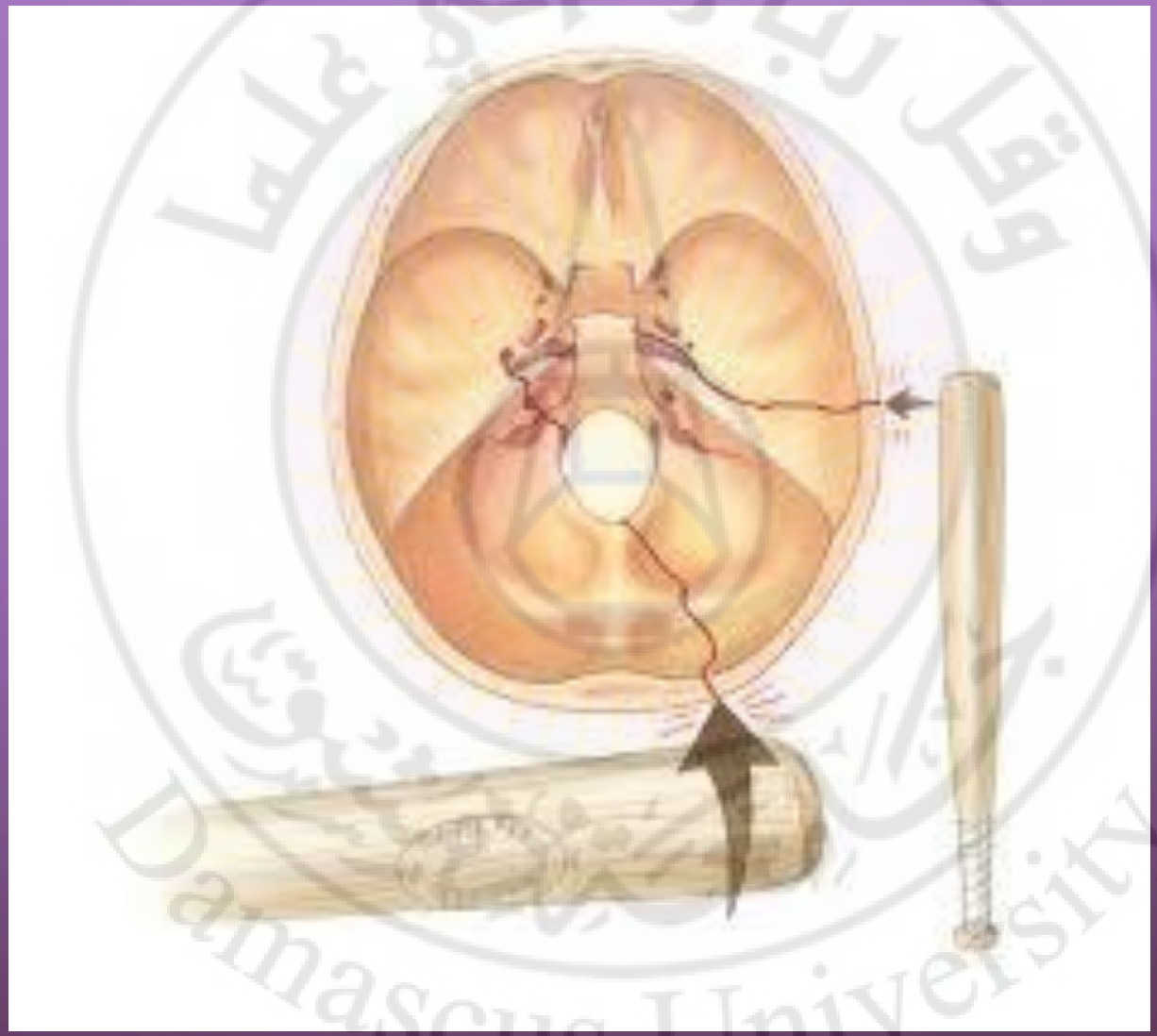
Subdural vs Epidural Hematoma

Subdural Hematoma



Epidural Hematoma

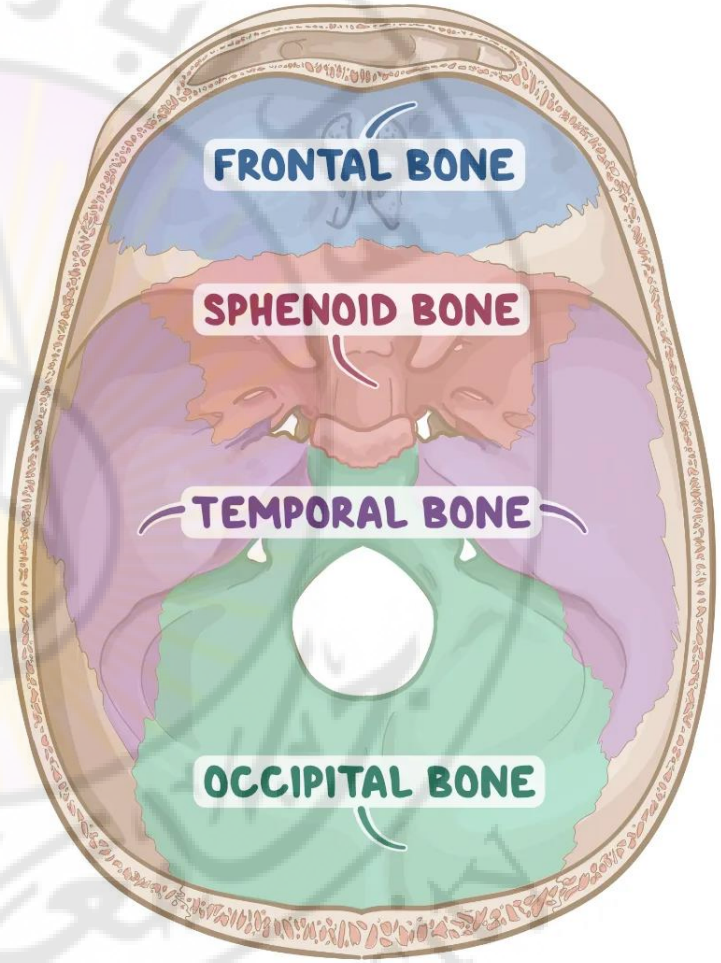


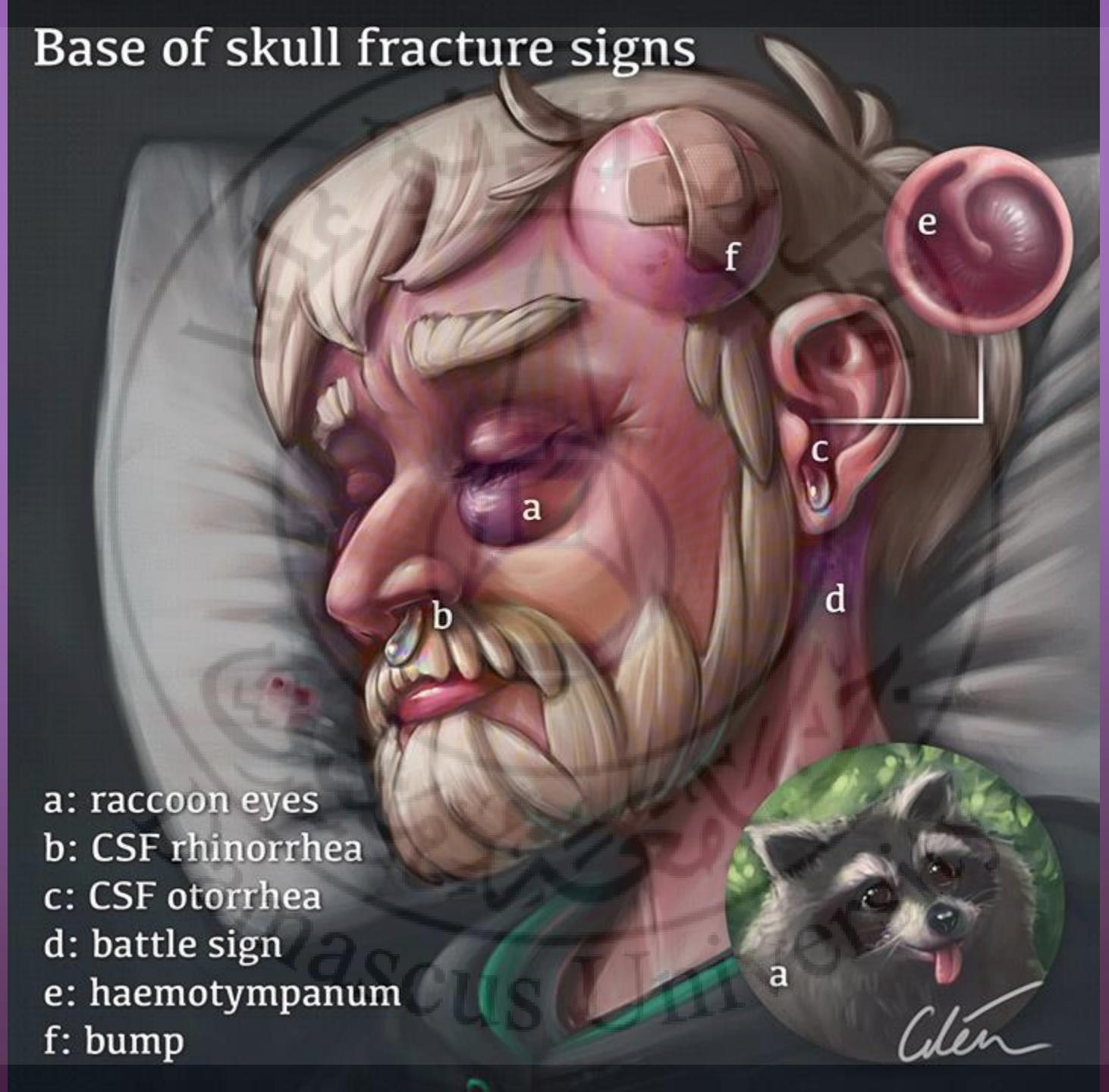


BACKGROUND

* TRAUMATIC HEAD INJURY INVOLVING a BREAK in at LEAST ONE of the BONES at **BASE** of **SKULL**
* SERIOUS & LIFE-THREATENING COMPLICATIONS

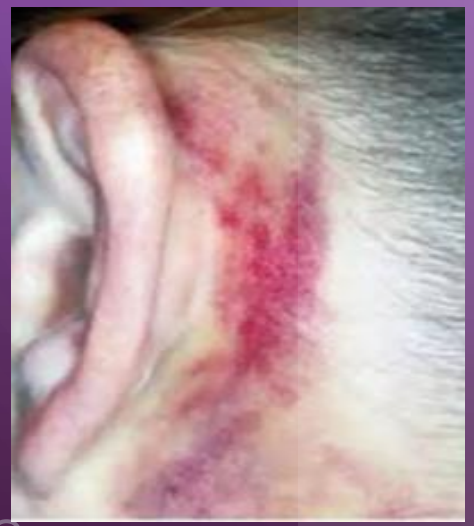
LOCATION (FOSSA)	SIGNS & SYMPTOMS
ANTERIOR	~ "RACCOON EYES" ~ "HALO" SIGN ~ PARTIAL/TOTAL LOSS of VISION/SMELL ~ EYE MOVEMENT DEFECTS
MIDDLE	~ DAMAGE to CAROTID A. ~ HEARING LOSS ~ LOSS of BALANCE ~ BATTLE SIGN
POSTERIOR	~ CERVICAL SPINE INJURY ~ VERTEBRAL A. INJURY ~ DAMAGE to LOWER CRANIAL N.

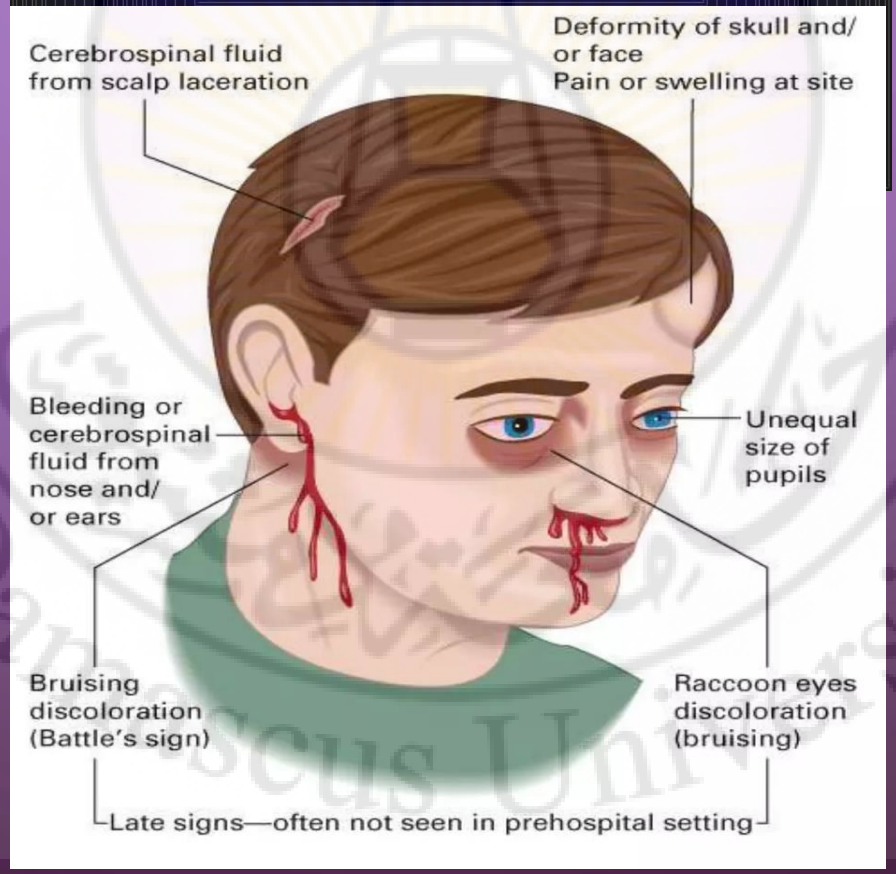


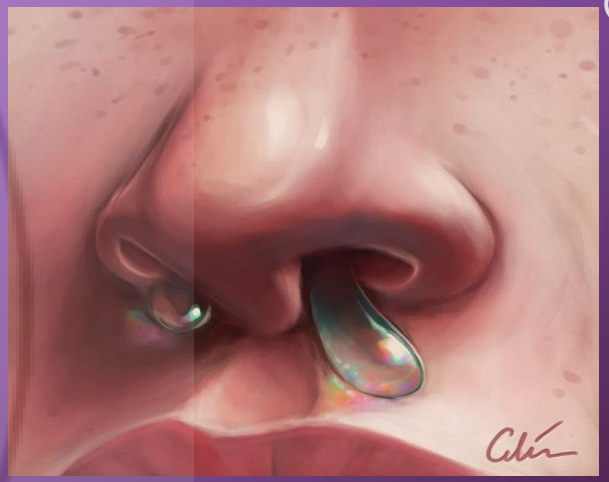

Base of skull fracture signs
f
e
c
a
b
d
a: raccoon eyes
b: CSF rhinorrhea
c: CSF otorrhea
d: battle sign
e: haemotympanum
f: bump
a

Other NeuroExam

- Signs of Skull Base fracture
  - Raccoon eyes
  - Battle sign (after 8-12 h)
  - CSF rhinorrhea or otorrhea
  - Hemotympanum







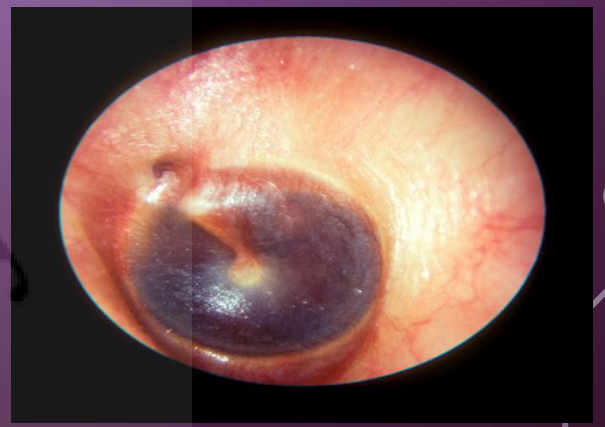
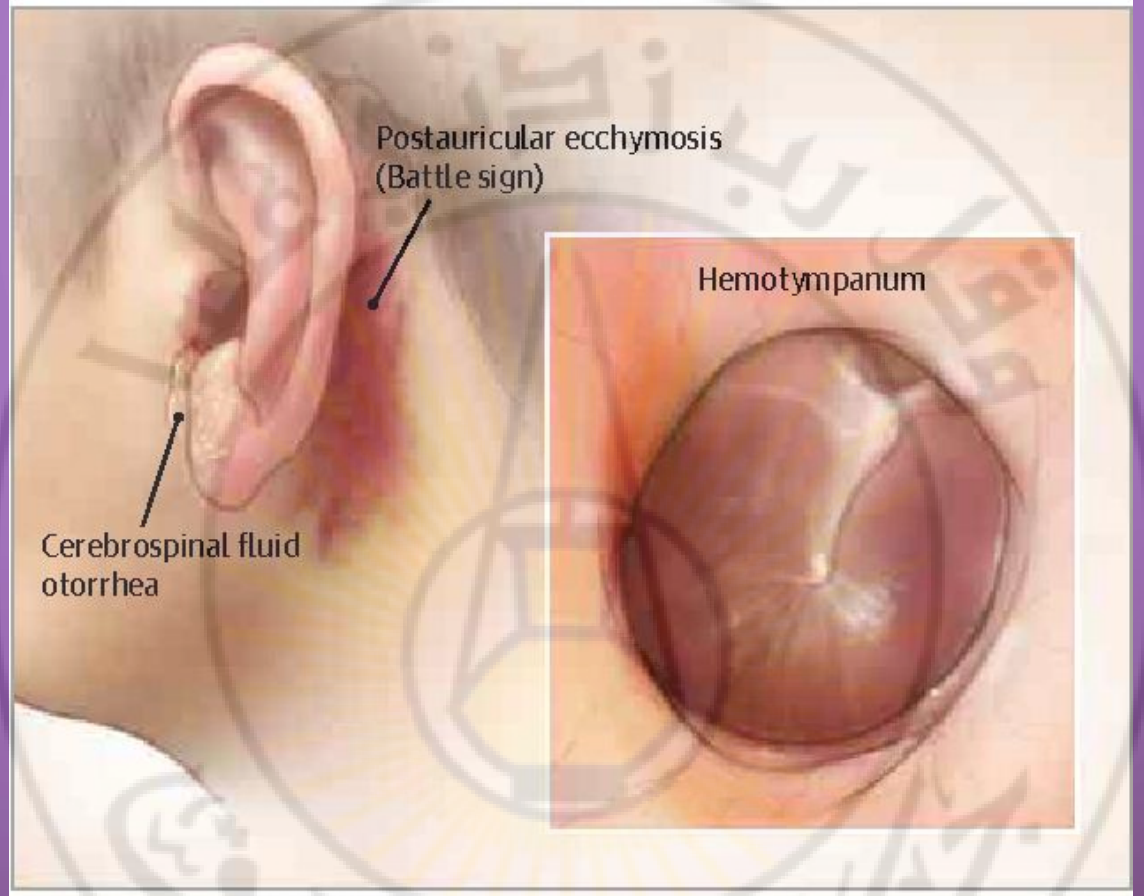


Figure 1. Signs of Basilar Skull Fracture



TEST TO DETERMINE CSF LEAKAGE

- Method 2(halo ring sign).
- Allow leaking fluid drip onto an absorbent material (white pad/towel).
- Observes the drainage
- Within a few minutes the blood coalesces into center and a yellowish ring encircles the blood.

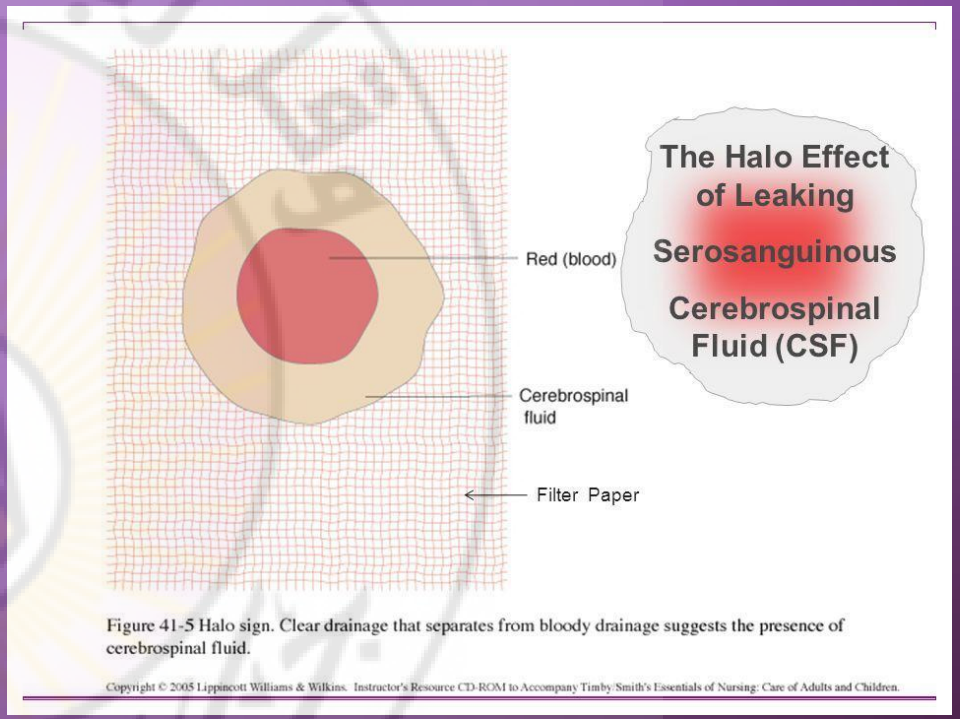
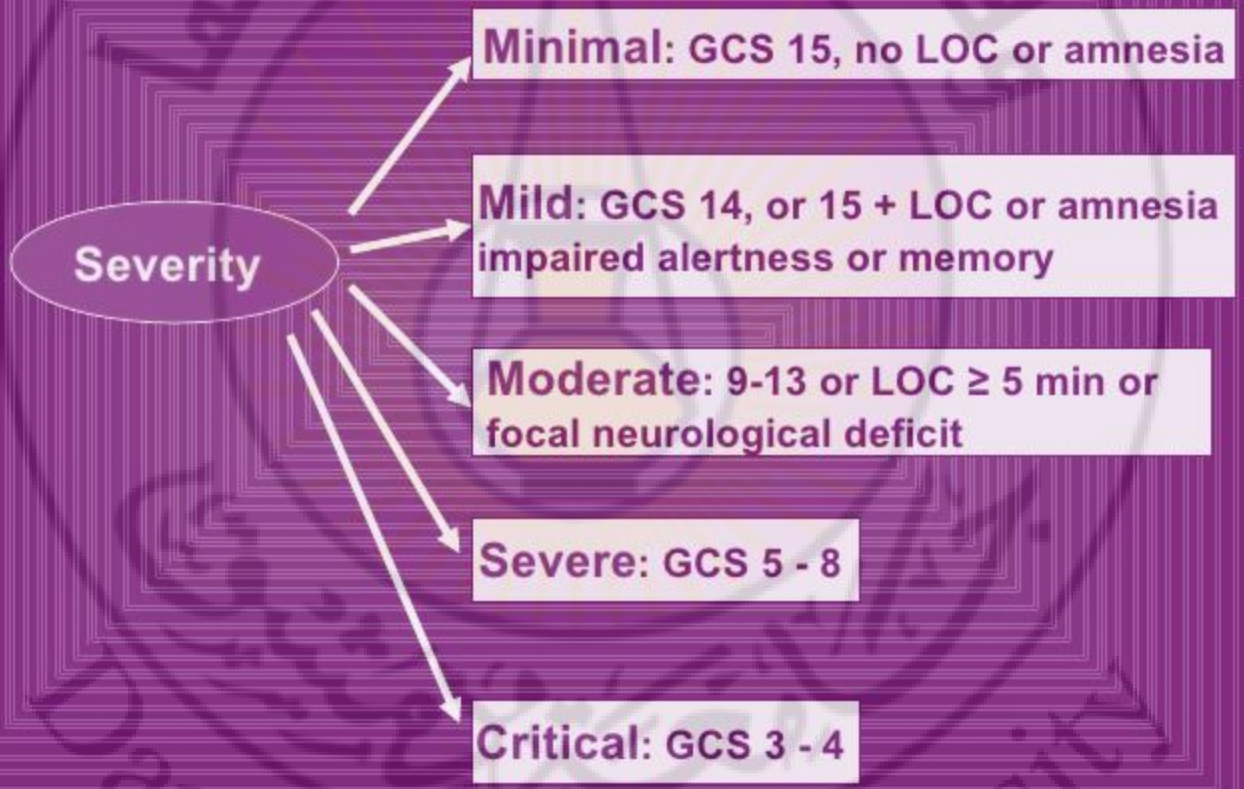


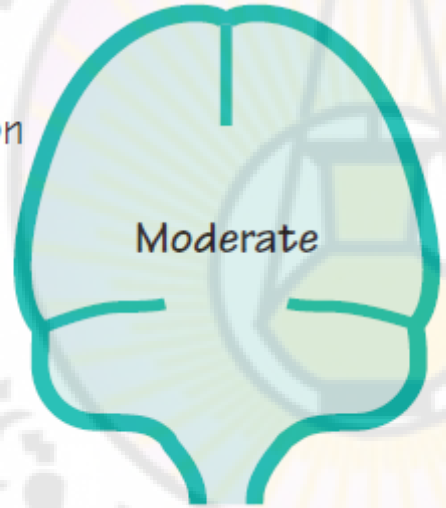
Figure 41-5 Halo sign. Clear drainage that separates from bloody drainage suggests the presence of cerebrospinal fluid.

Classification

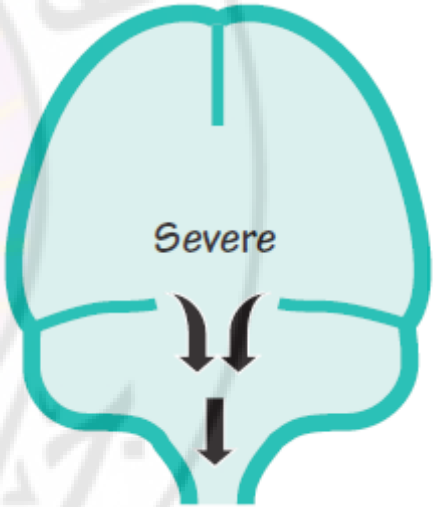


Primary injury

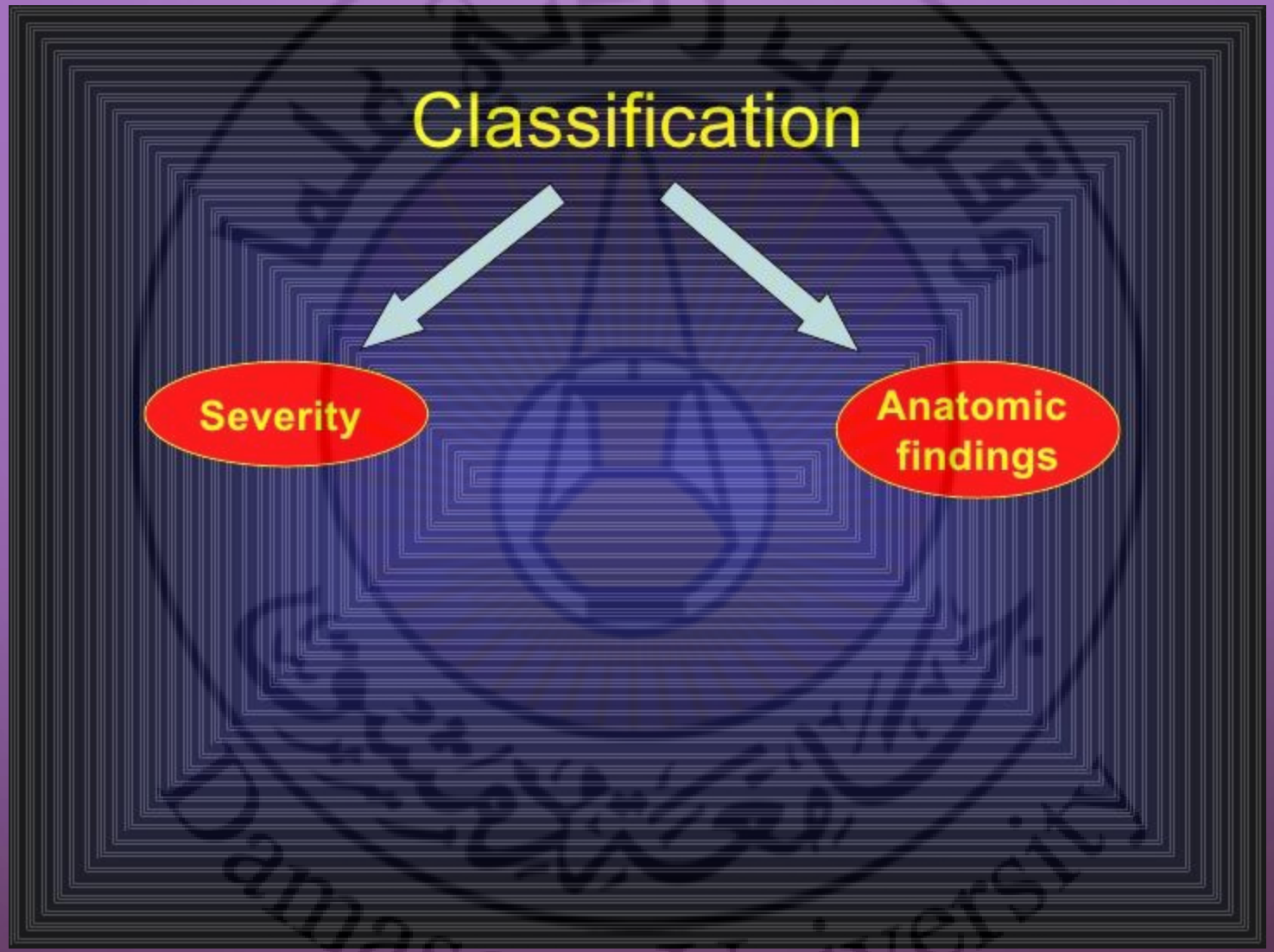
Concussion, or concussion plus some retrograde and post-traumatic amnesia

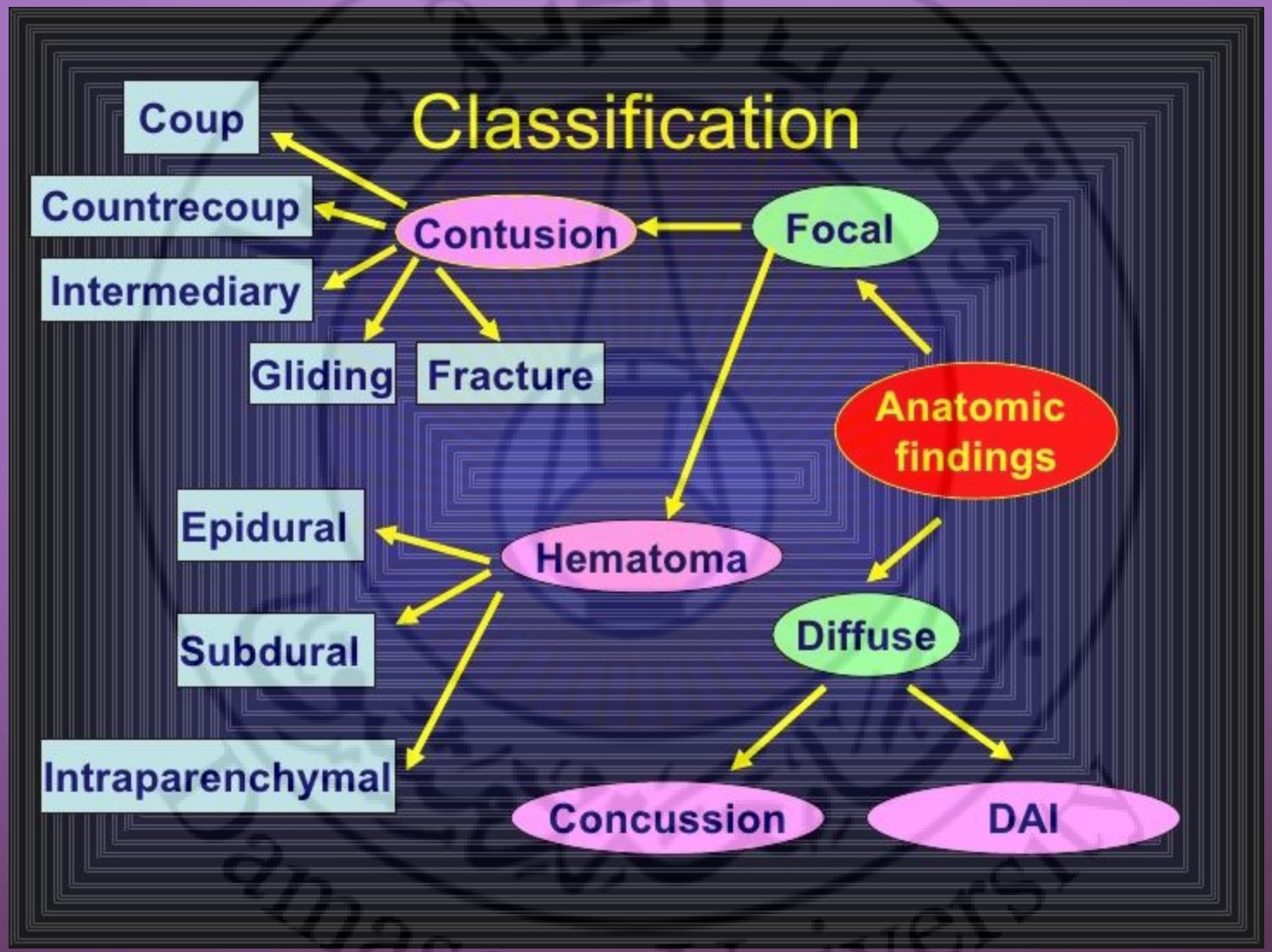


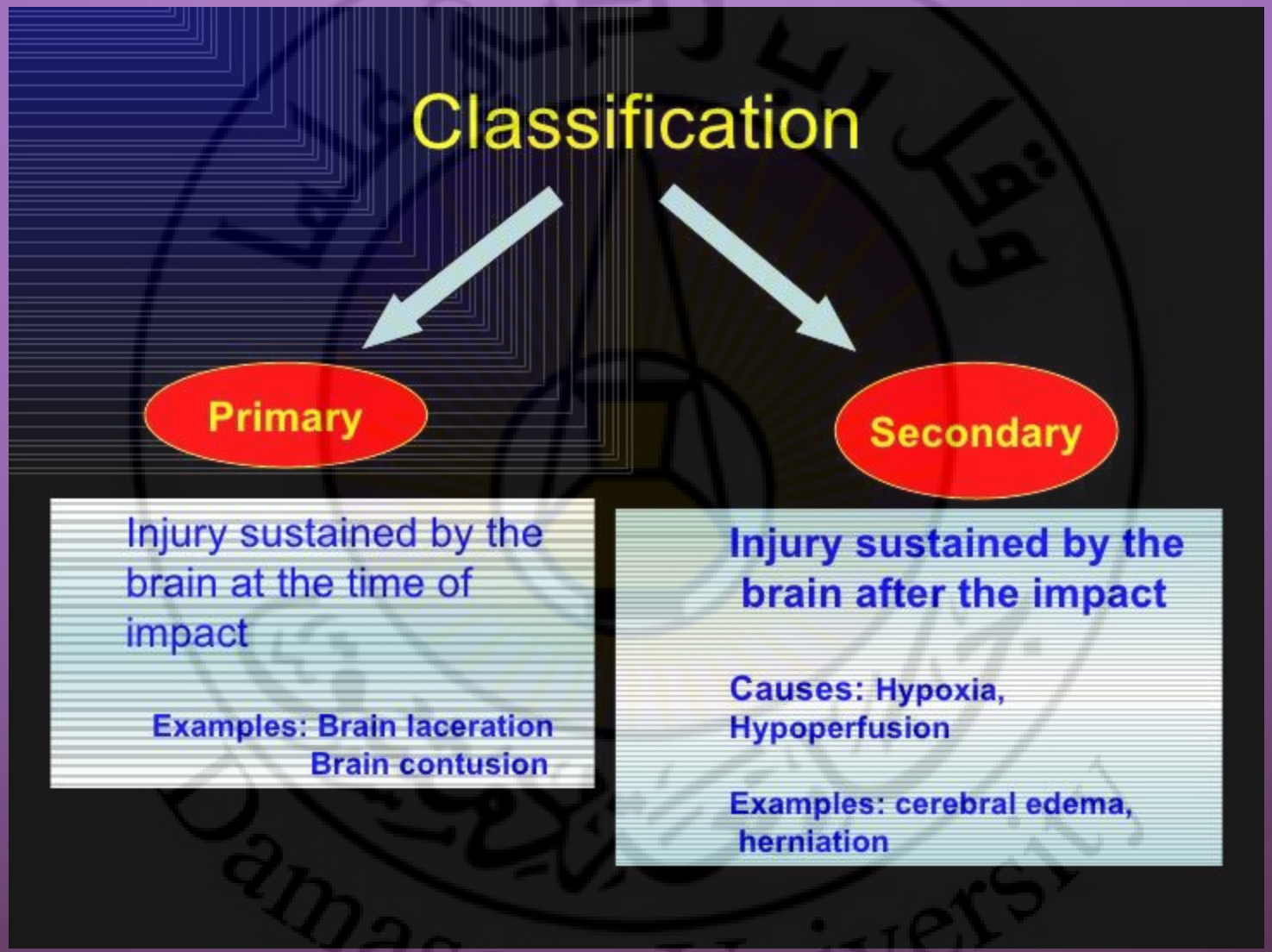
Persistent coma after the accident with fairly good scores on the Glasgow Coma Scale, and no signs of brainstem malfunction



Persistent coma after the accident, poor scores on the Glasgow Coma Scale, and evidence of failing brainstem function


Classification
Severity
Anatomic findings


Classification
Coup
Countrecoup
Contusion
Intermediary
Gliding
Fracture
Focal
Anatomic findings
Epidural
Hematoma
Subdural
Intraparenchymal
Diffuse
Concussion
DAI


Classification
Primary
Secondary
Injury sustained by the brain at the time of impact
Examples: Brain laceration
Brain contusion
Injury sustained by the brain after the impact
Causes: Hypoxia, Hypoperfusion
Examples: cerebral edema, herniation

Management

The first question, near or at the site of the head injury, is whether there is any indication for assessment in the hospital emergency department

A Airway
Clear airway, with cervical spine control until cervical injury is confidently excluded

B Breathing
Assess ventilation and chest movement. Arterial blood gases

C Circulation
Assess likelihood of blood loss. Monitor BP and P frequently. Establish IV line

D Dysfunction of CNS
Assess by Glasgow Coma Scale at frequent intervals

E Exposure
Identify all injuries, head to toe, front and back

Indications for hospital assessment after head injury

- Any loss of consciousness, amnesia or fall in the Glasgow Coma Scale at any time.
- Any focal neurological symptom or sign.
- Suspicion of skull fracture or penetrating injury.
- Seizure, vomiting or persistent headache.
- Current drug or alcohol intoxication (making assessment unreliable).
- High-energy head injury (e.g. pedestrian struck by car; thrown from moving vehicle; fall downstairs; fall of 1 metre or more onto head).
- Coagulopathy (history of bleeding or clotting disorder or anticoagulated).
- Previous neurosurgery.
- Suspicion of non-accidental injury.
- Age 65 years or more.

Indications for CT brain scan after head injury

- GCS less than 13 at any time, or 13–14 at 2 hours after injury.
- Suspected skull fracture or penetrating head injury
- Post-traumatic epileptic seizure.
- Focal neurological deficit.
- More than one episode of vomiting (except perhaps in children).
- Amnesia for more than 30 minutes of events prior to impact.
- Any loss of consciousness or amnesia if also:
  —aged 65 years or older;
  —coagulopathy;
  —high-energy head injury.

Reasons to talk to a neurosurgeon

- New and potentially significant abnormality on CT brain scan.
- Persisting coma (GCS of 8 or less) after initial resuscitation.
- Unexplained confusion (for more than 4 hours).
- Falling GCS (especially falling motor score).
- Progressive focal neurological deficit.
- Epileptic seizure without full recovery.
- Penetrating injury.
- CSF leak.

Head injury may result from:

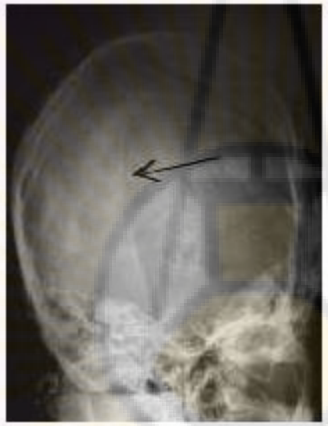
- stroke
- cerebral haemorrhage
- epilepsy
- cardiac dysrhythmia
- alcoholic intoxication
- non-accidental injury to children

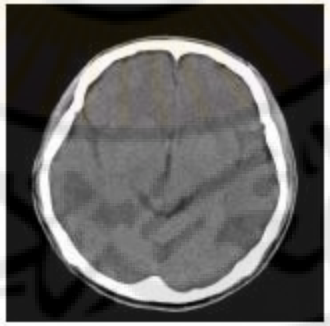
Reasons to suspect a skull fracture or penetrating head injury

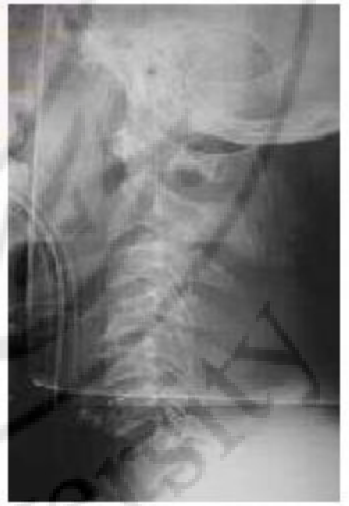
- Clear fluid (CSF) running from nose
- Blood or clear fluid running from ear(s)
- Bruising around eye(s) with no eye trauma (panda eyes)
- Bruising behind ear(s) (Battle's sign)
- New unilateral deafness
- Significant visible scalp or skull wound

Imaging of head injury

- Modalities
  - Skull X-ray
  - CT scan
  - MRI
- Areas
  - Skull, brain
  - Cervical spine
  - Chest
  - Pelvis








MANAGEMENT
TRAINING
SKILLS
EMOTIONAL
COMMITMENT
INNOVATION
STRENGTH
TEAM
LEADERSHIP
MISSION
RISK
CONDUCT
TRUST
COMMERCE

Figure 1 Example of an observation chart

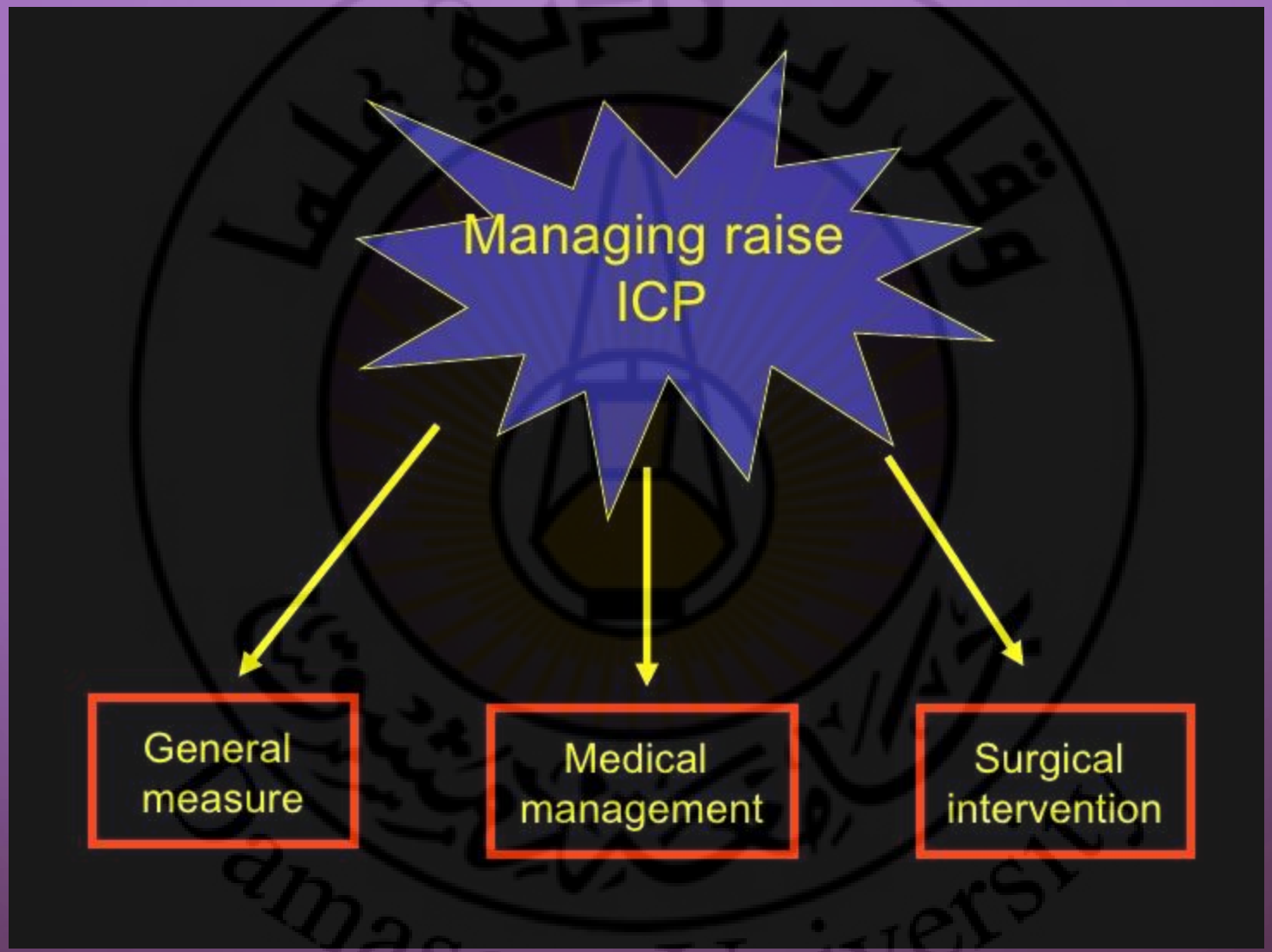
Time observations are made				Notes
Glasgow Coma Scale	Eyes open	Spontaneously To speech To pain None		Eyes closed by swelling = C
	Best verbal response	Orientated Confused Inappropriate words Incomprehensible sounds None		Endotracheal tube or tracheotomy = T
	Best motor response	Obey commands Localise pain Withdraws from pain Flexion to pain Extension to pain None		Usually record the best arrival response
	Total score			
Temperature (°C)		40 39 38 37 36 35		
Blood pressure and pulse rate		200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30		Pupil scale (mm) 1 2 3 4 5 6 7 8
Respiration				
Pupils	Right	Size Reaction		Reaction = + No reaction = – Eye closed = c
	Left	Size Reaction		
Limb movement	Arms	Normal power Mild weakness Severe weakness Spastic flexion Extension No response		If there is a difference between limb movements on the right and left sides, record separately and indicate as L and R
	Legs	Normal power Mild weakness Severe weakness Spastic flexion Extension No response		

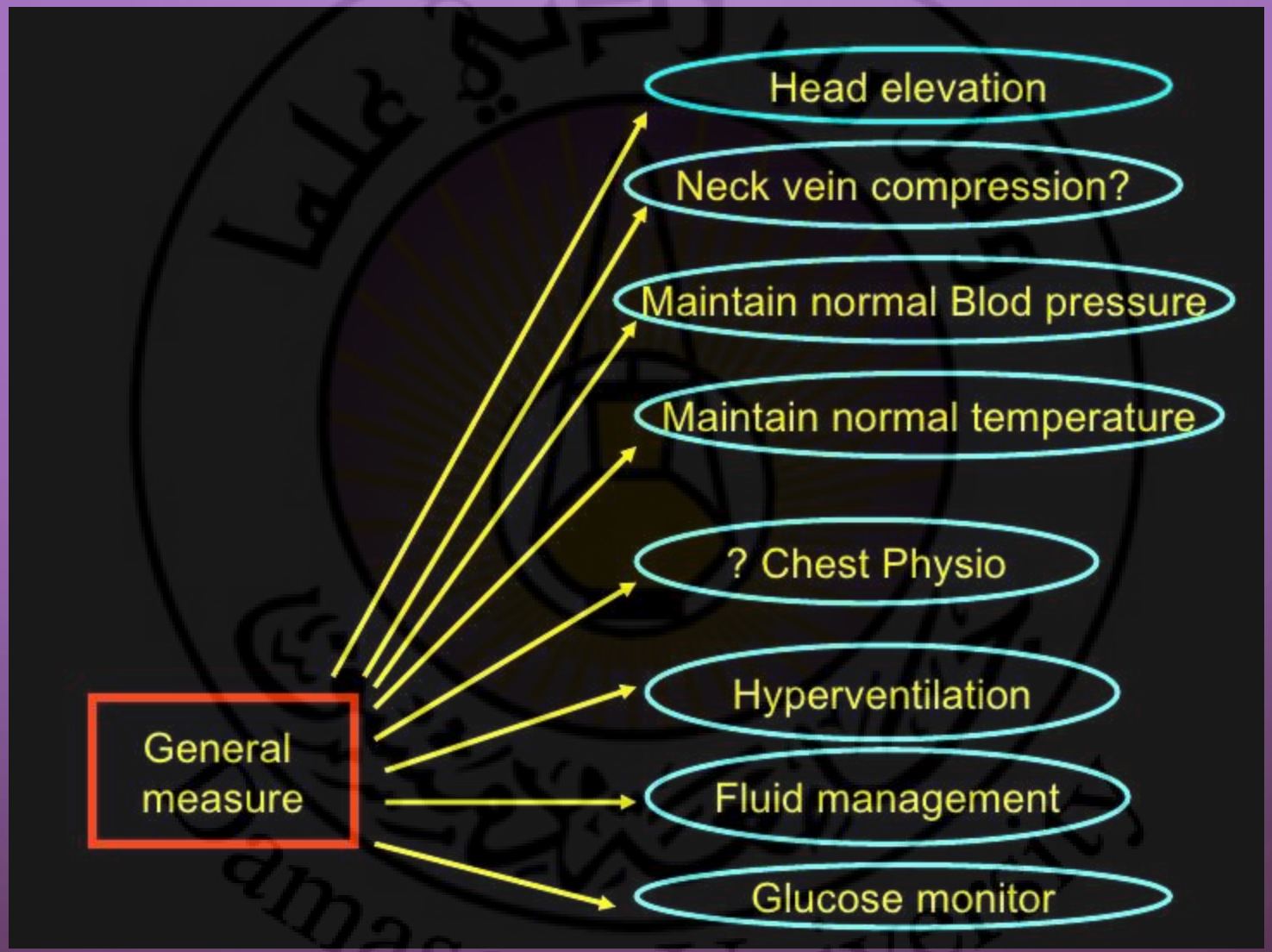
Prehospital management

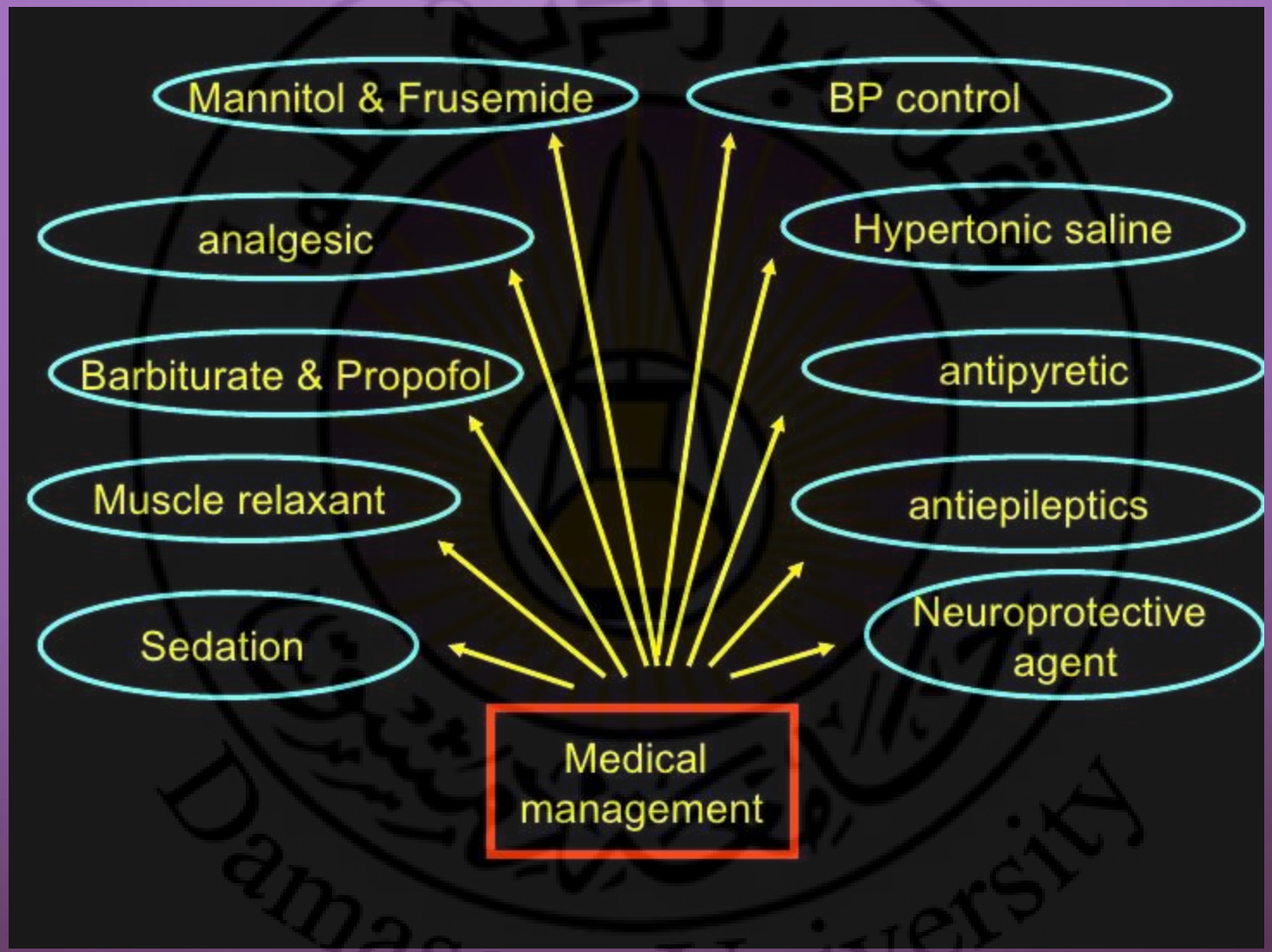
How to transfer head injury patient:

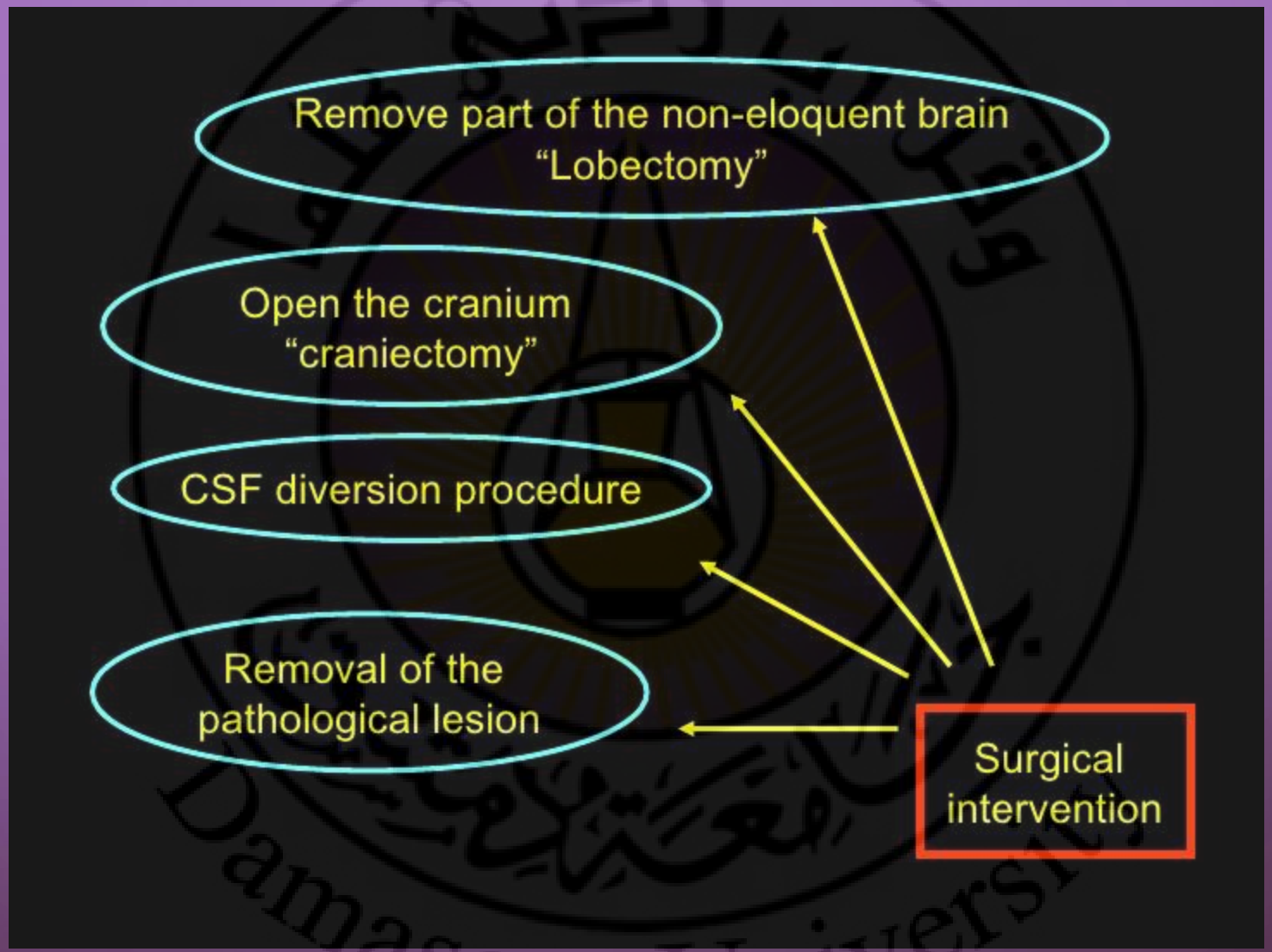
- Stabilize patient at trauma scene
- Do not move patient unnecessarily
- Maintain ABC, ABC, ABC, ABC
- Protect cervical spine
- Stop active bleeding
- Relay information to receiving doctors
  - ABC status
  - GCS & pupil size
  - Suspected injuries

- Transfer patient only if it is SAFE


Managing raise ICP
General measure
Medical management
Surgical intervention


Head elevation
Neck vein compression?
Maintain normal Blod pressure
Maintain normal temperature
? Chest Physio
Hyperventilation
Fluid management
Glucose monitor
General measure


Mannitol & Frusemide
BP control
analgesic
Hypertonic saline
Barbiturate & Propofol
antipyretic
Muscle relaxant
antiepileptics
Sedation
Neuroprotective agent
Medical management


Remove part of the non-eloquent brain
“Lobectomy”
Open the cranium
“craniectomy”
CSF diversion procedure
Removal of the
pathological lesion
Surgical
intervention

Initial features:

- level of consciousness
- skull fracture
- focal neurological signs

Secondary features:

- epilepsy
- intracranial haematoma
- meningitis

Duration:

- of coma
- of post-traumatic amnesia
- of stay in hospital

Persisting deficits:

- intellectual
- psychological
- focal neurological

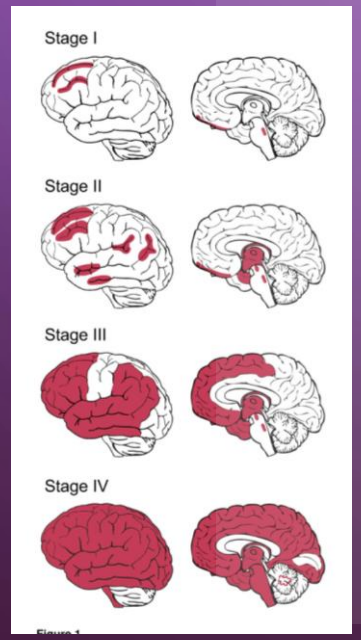
Post-concussion syndrome

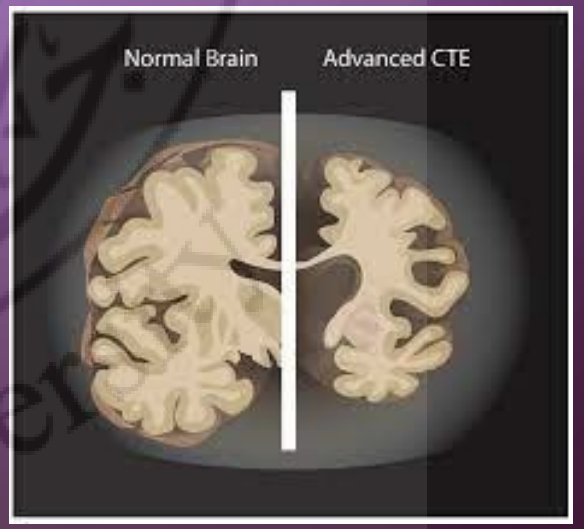
- Headache
- Dizziness
- Impaired concentration
- Impaired memory
- Fatigue
- Anxiety
- Depression
- Irritability
- Indecisiveness
- Impaired self-confidence
- Lack of drive
- Impaired libido

Chronic traumatic encephalopathy

"Punch Drunk"

First-stage symptoms are confusion, disorientation, dizziness, and headaches.
Second-stage symptoms include memory loss, social instability, impulsive behavior, and poor judgment.
Third and fourth stages include progressive dementia, movement disorders, hypomimia, speech impediments, sensory processing disorder, tremors, vertigo, deafness, depression and suicidality



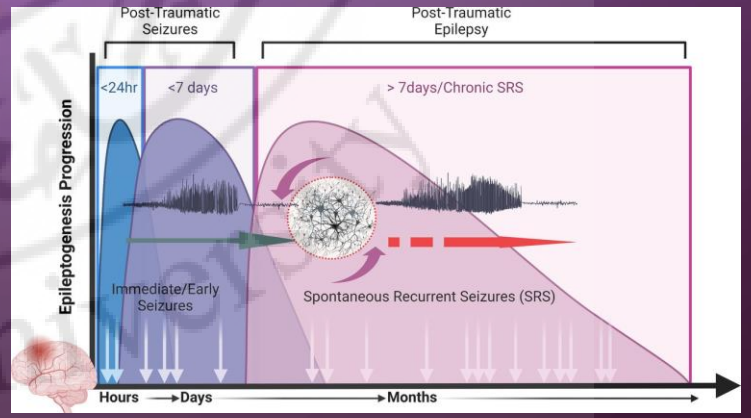


Post-traumatic epilepsy

Posttraumatic epilepsy shows its presence within a year of the accident in about 50% of patients who are going to develop this late complication of their head injury. In the rest, it may not occur for several years.

There are certain features of the head injury which make posttraumatic epilepsy more likely:

- post-traumatic amnesia lasting more than 24 hours;
- focal neurological signs during the week after the head injury;
- epilepsy during the week after the head injury;
- depressed skull fracture;
- dural tear;
- intracranial haematoma.



Outcome from severe head injury

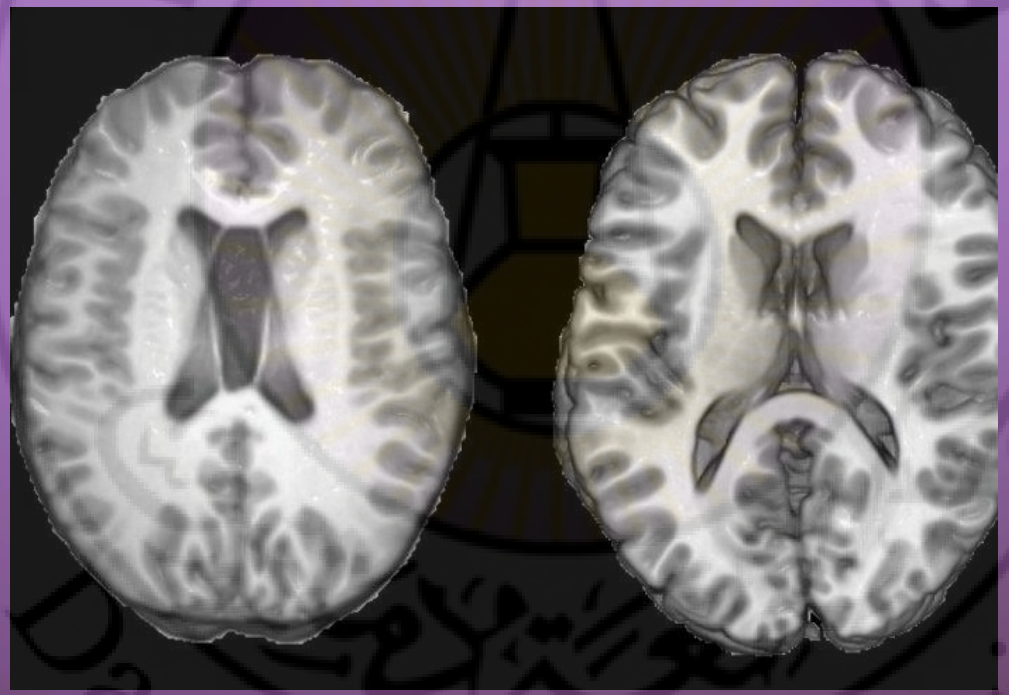
Mortality from severe head injury (coma lasting more than 6 hours) is of the order of 50%. Those who survive are likely to have deficits in some or all of the following areas, depending on
which parts of the brain have been most damaged:

- intellectual function;
- mood, behaviour, personality;
- speech and communication;
- vision;
- motor and sensory function in the limbs;
- post-traumatic epilepsy.

Most of a patient's recovery will have occurred within 6
months of the injury, though further slower improvement may
occur in the next 12–18 months.

Outcome from severe head injury

Head injury patients show signs of faster ageing in the brain



Head injuries are already known to increase the risk of age-related neurological conditions such as dementia later in life

“Your chronological age is not necessarily the best indicator of your health or how much longer you will live,” said Dr James Cole, who led the study, from the Department of Medicine at Imperial College London.

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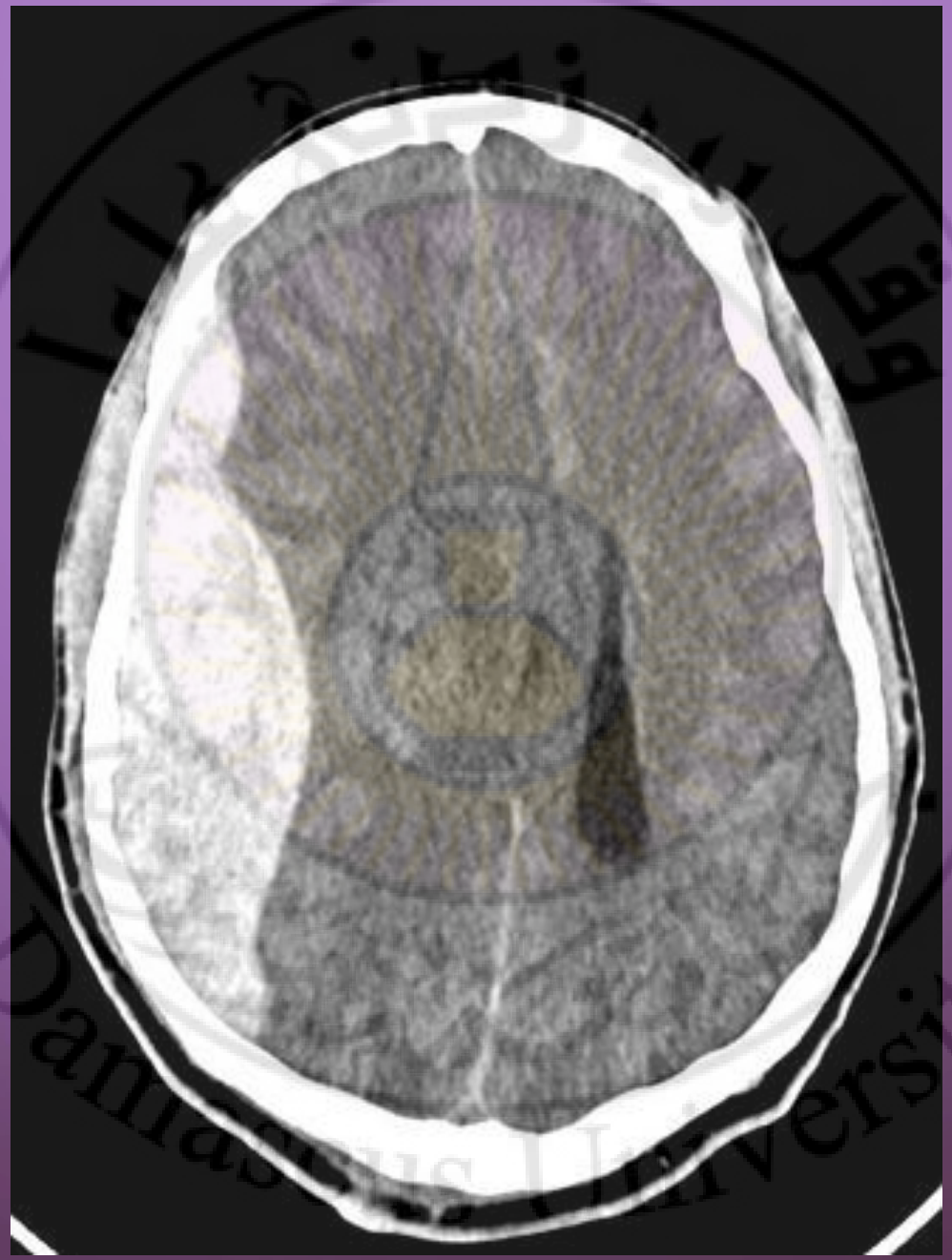

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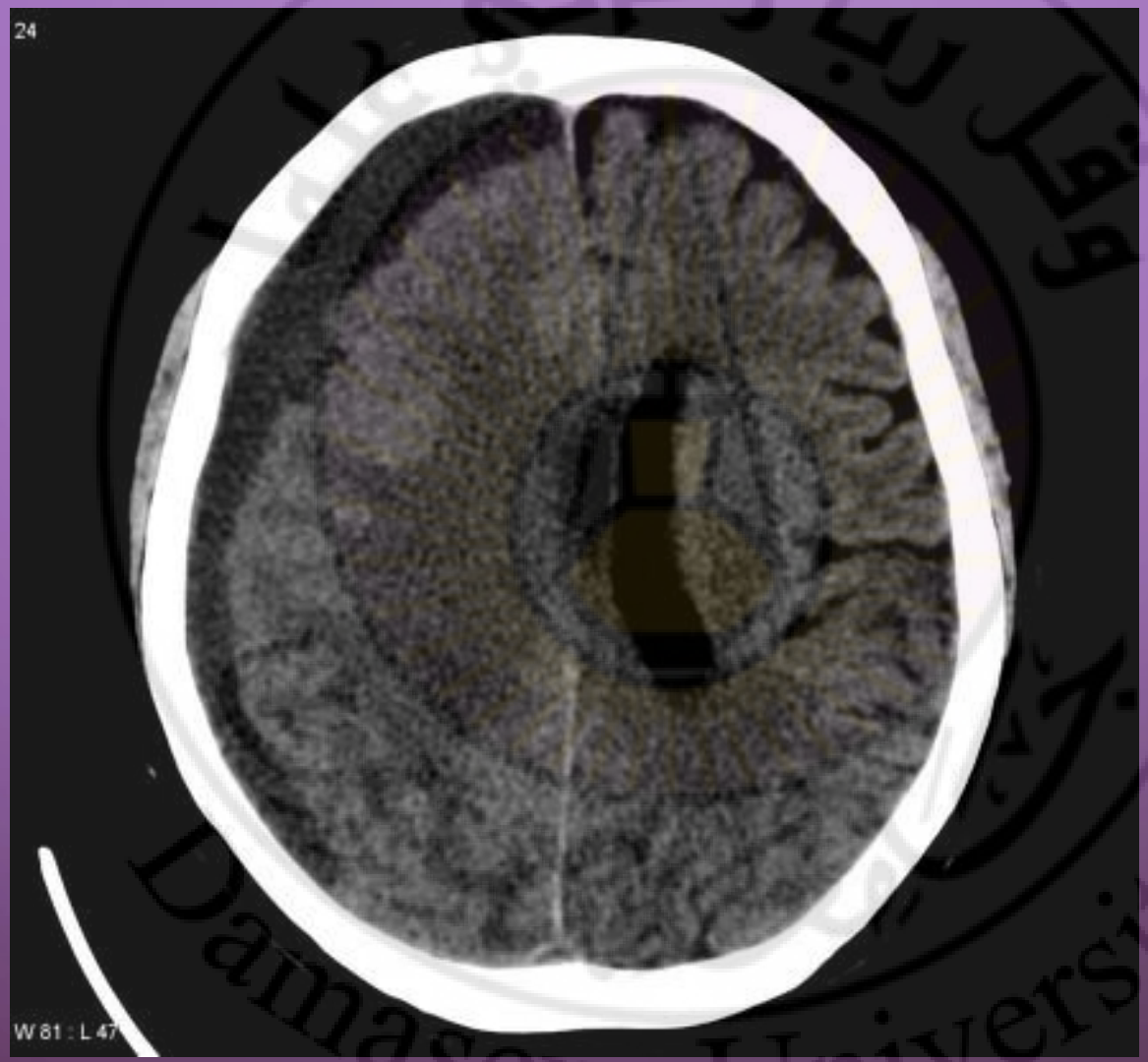

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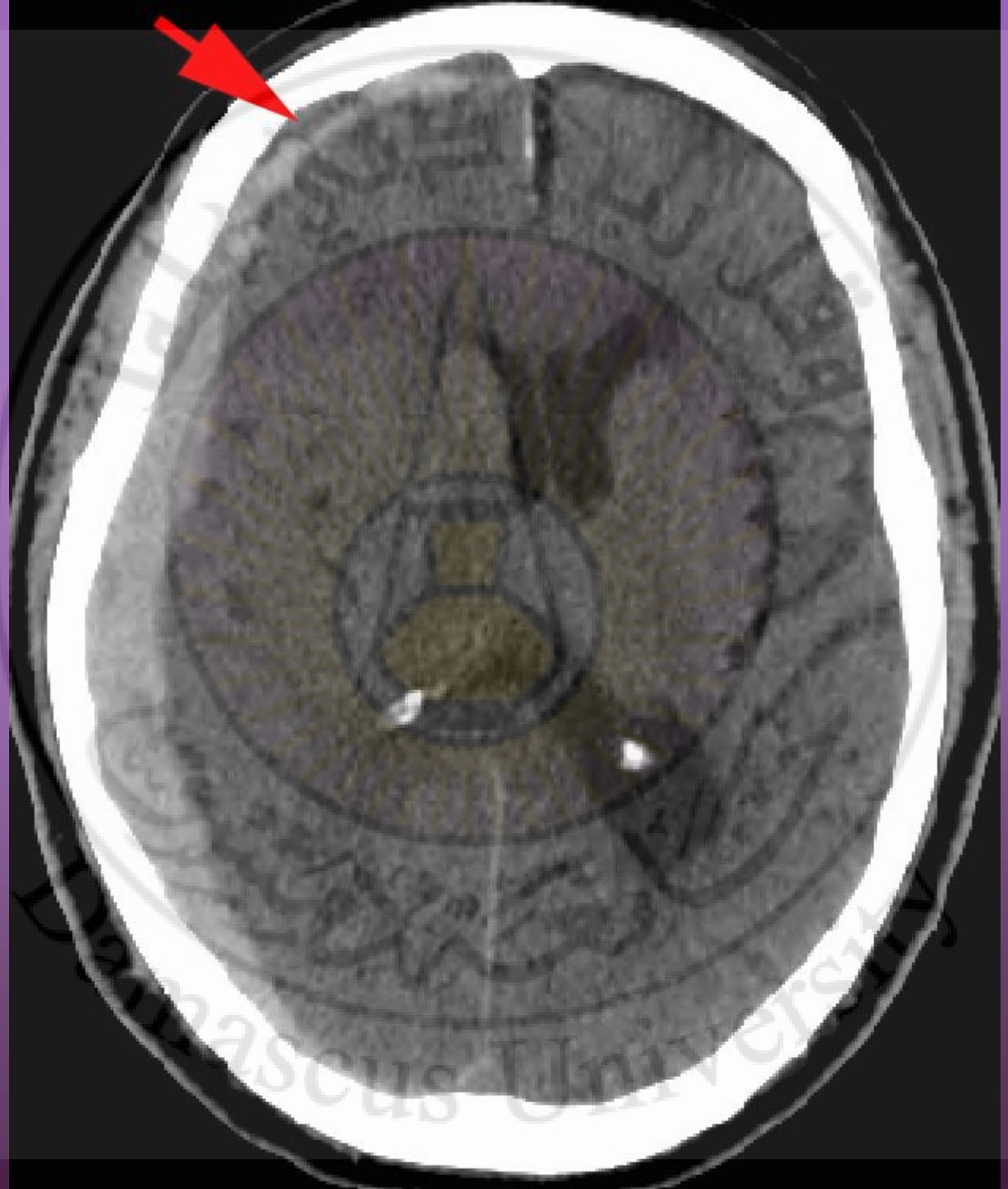

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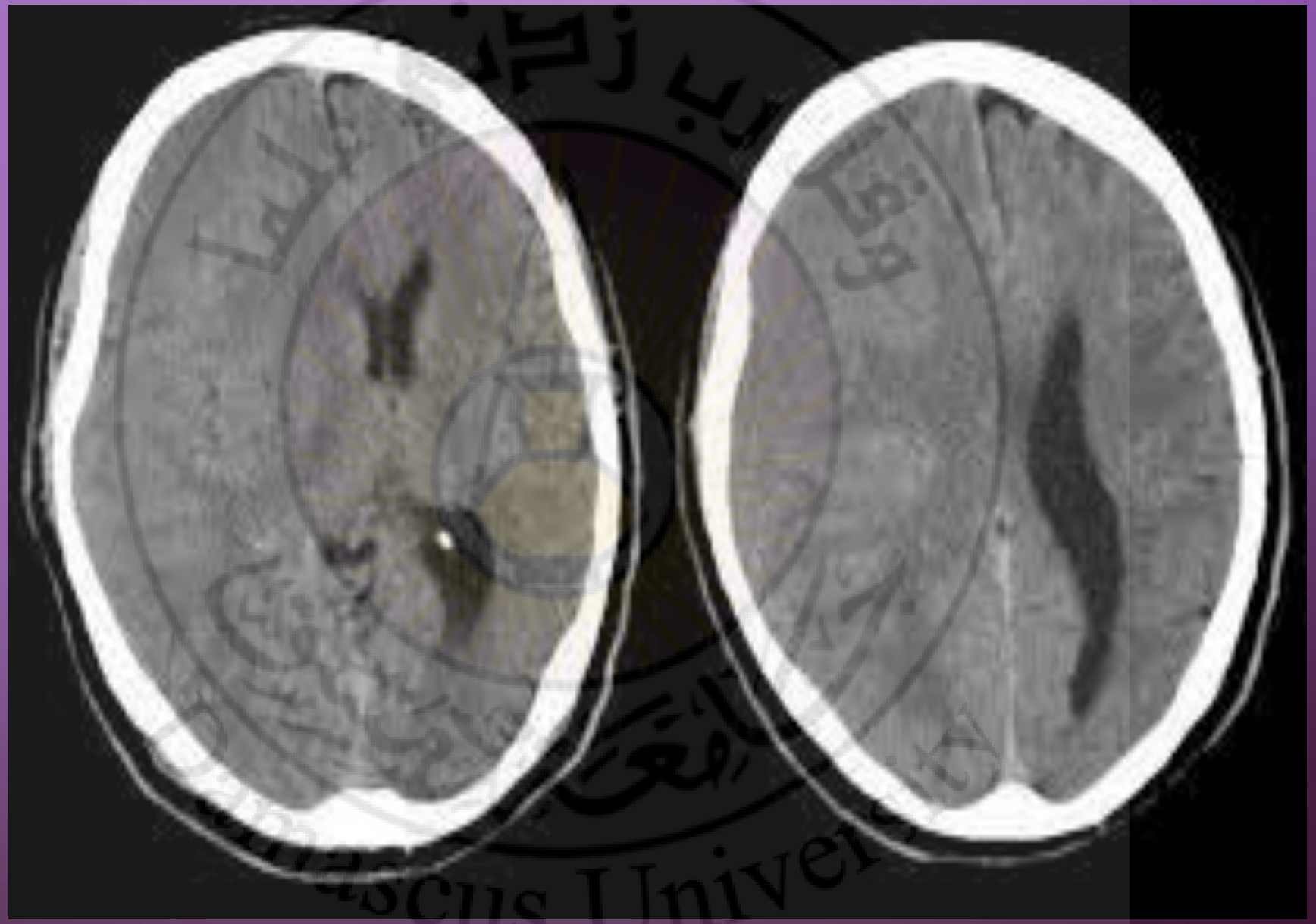

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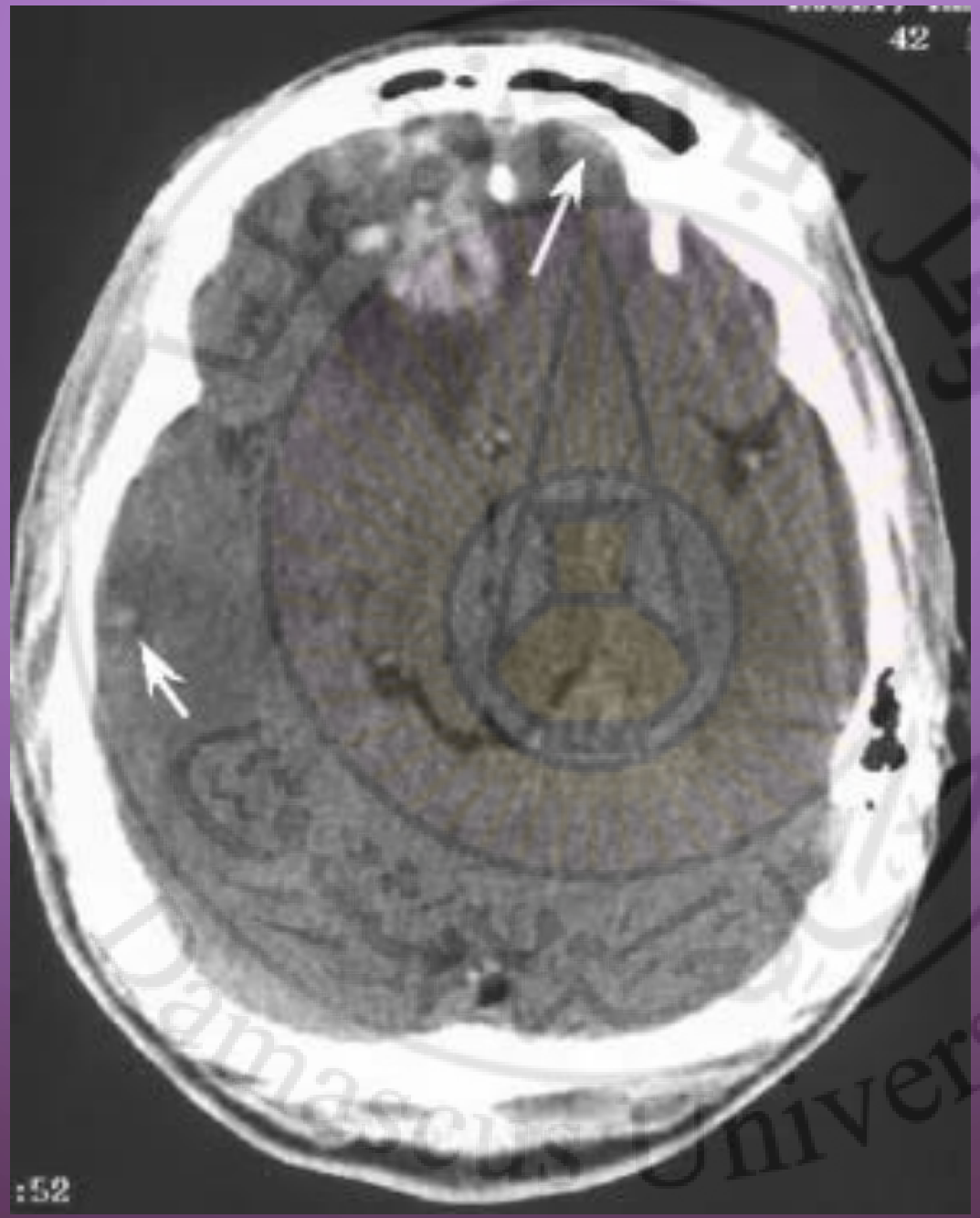

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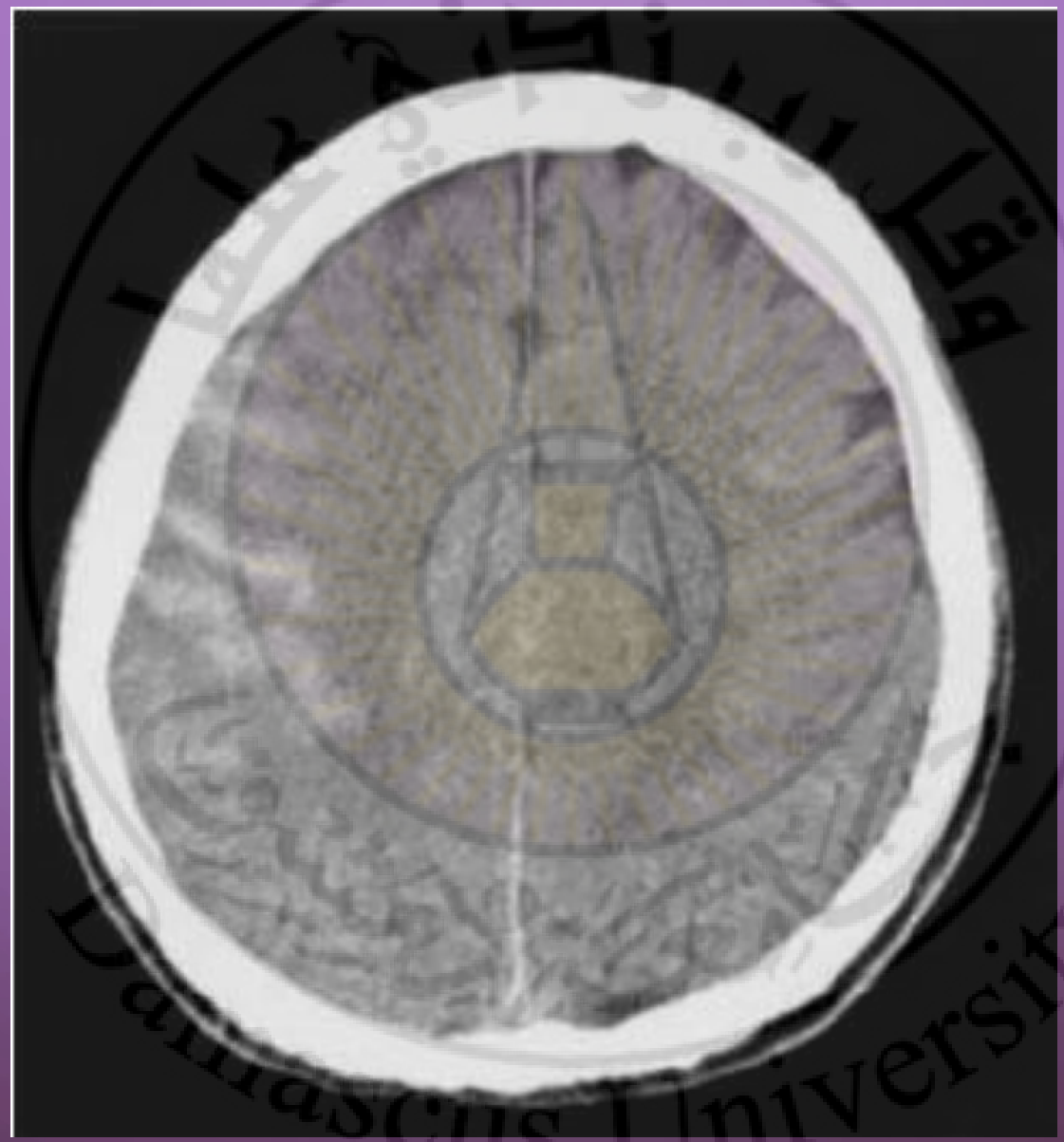

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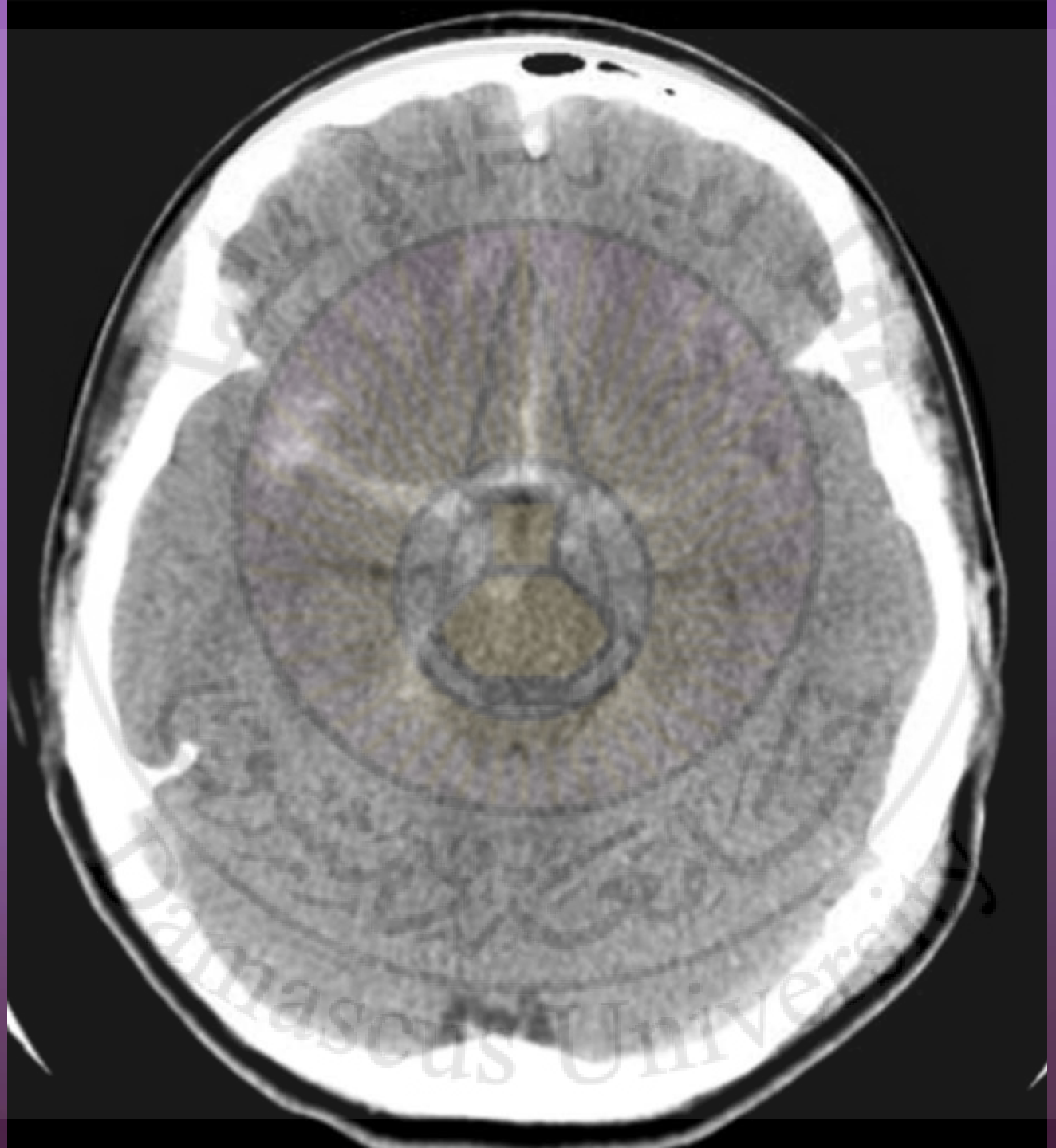
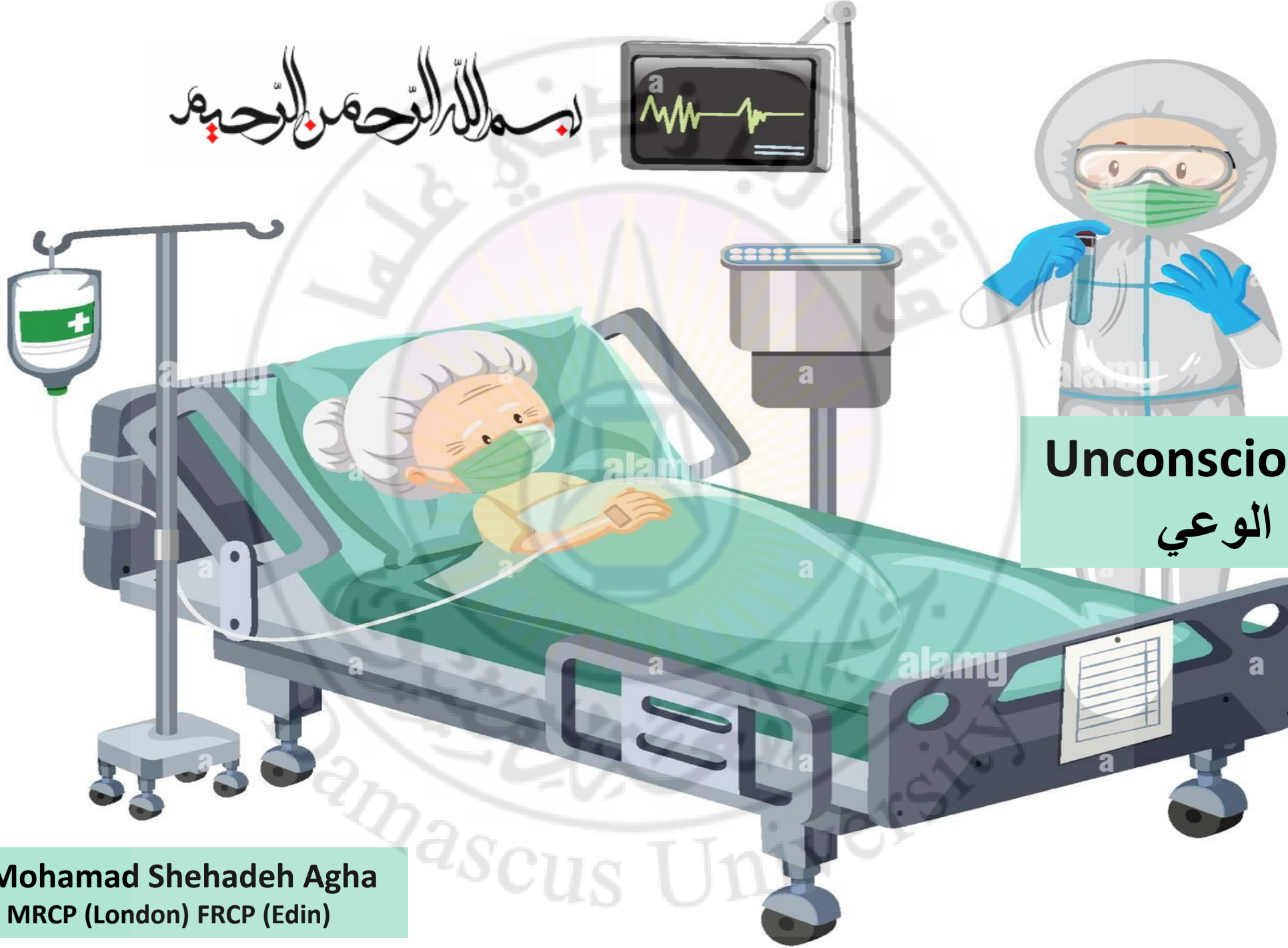


بسم الله الرحمن الرحيم



Unconsciousness
فقد الوعي

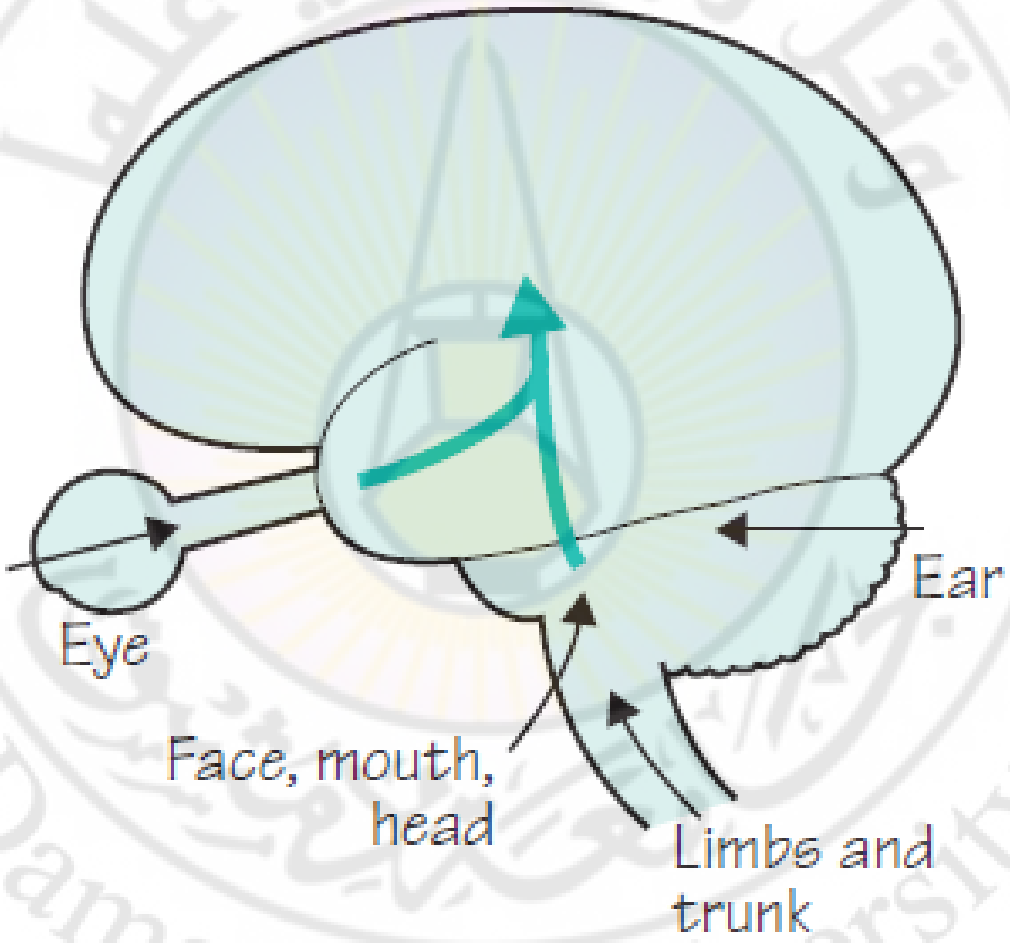
Prof. Mohamad Shehadeh Agha
MD MRCP (London) FRCP (Edin)

التعريف

الوعي هو حالة الادراك للذات والبيئة المحيطة

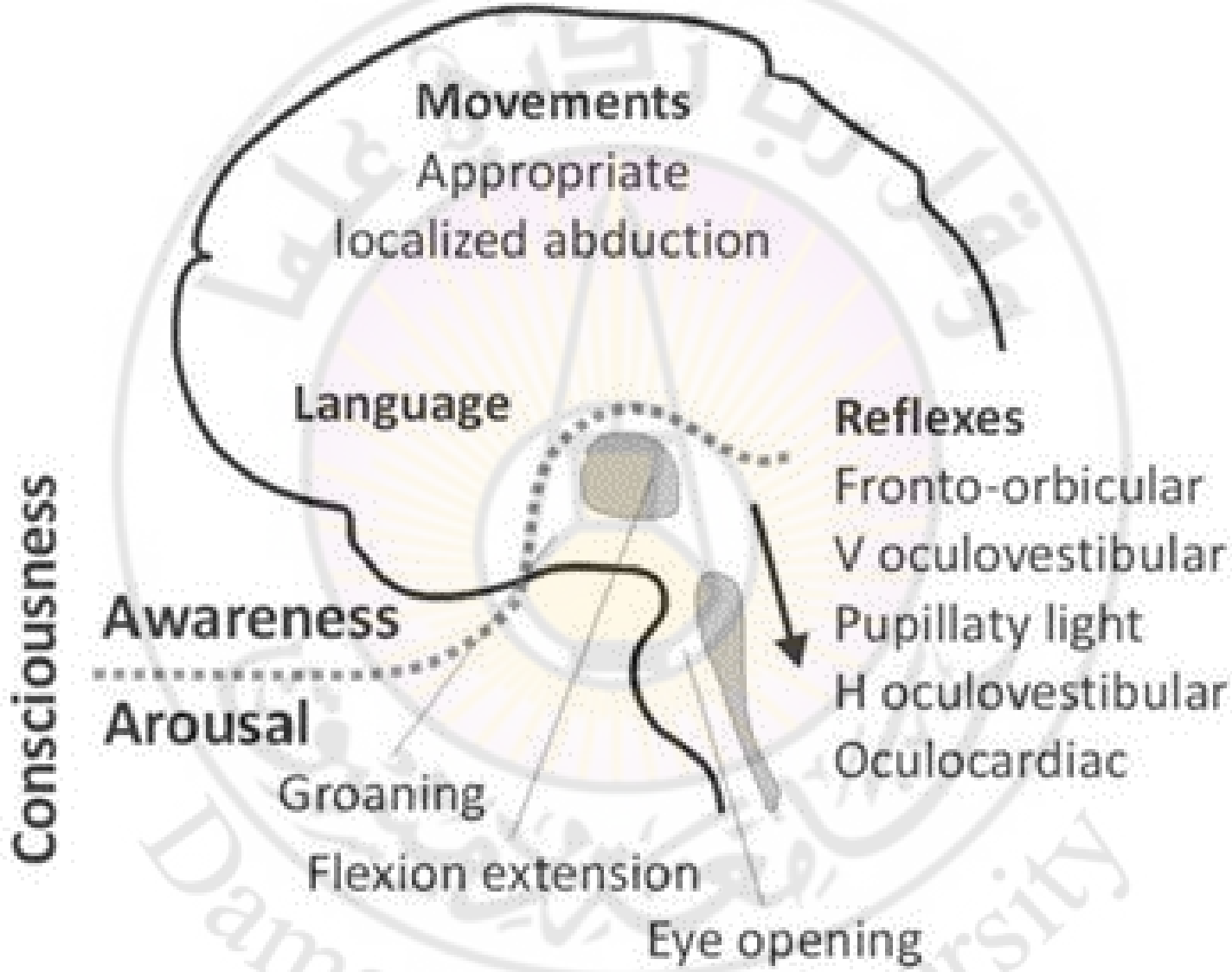
السبات هو العكس أي هو الغياب الكامل للإدراك للذات والبيئة المحيطة حتى عندما ينبه الشخص خارجيا

Important factors maintaining consciousness.

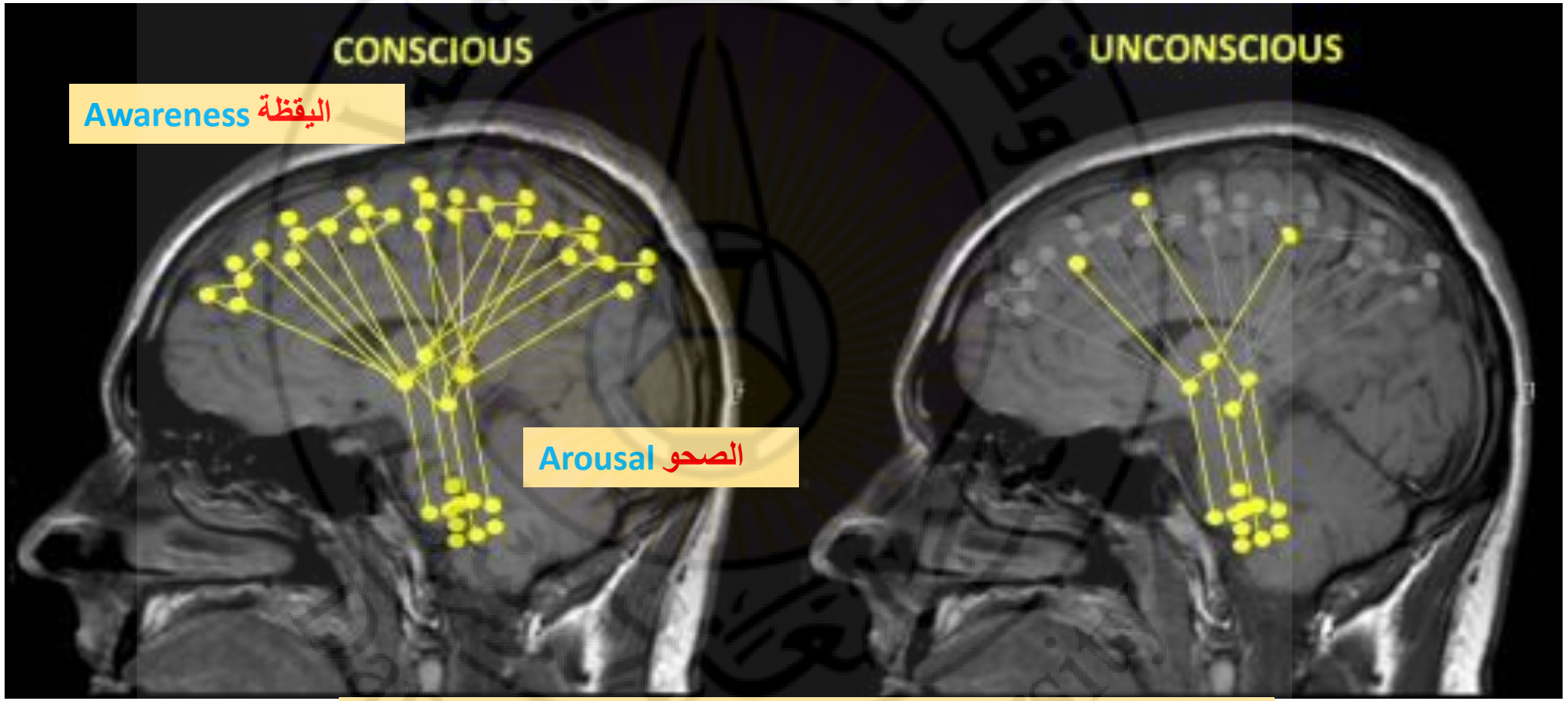


Awareness اليقظة

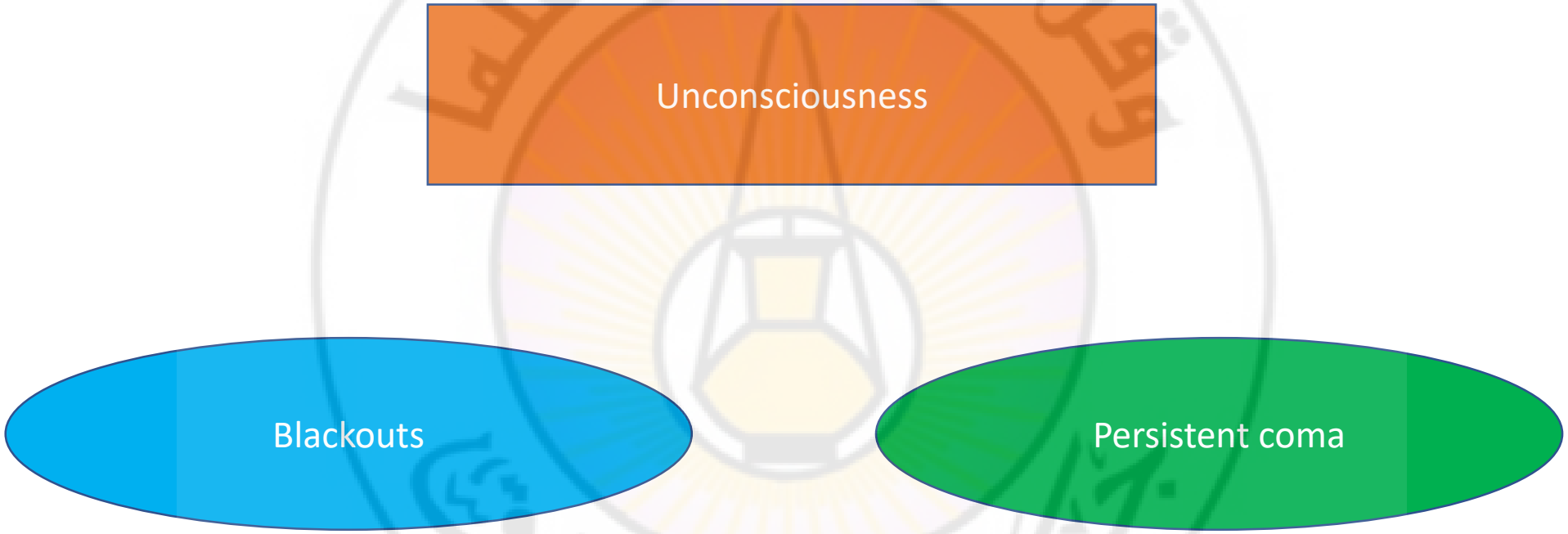
Arousal الصحو



Consciousness



State of full awareness of the self and one's relationship to the environment


Unconsciousness
Blackouts
Persistent coma

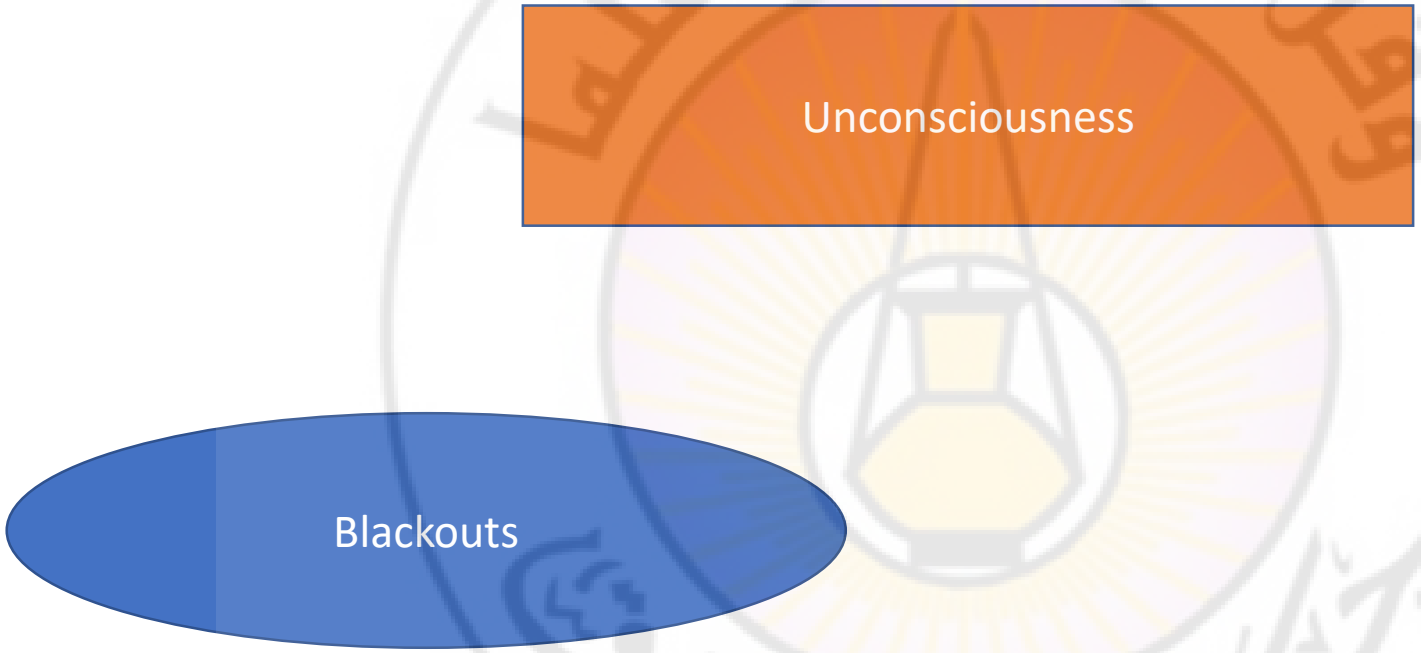
To define the story inquire about

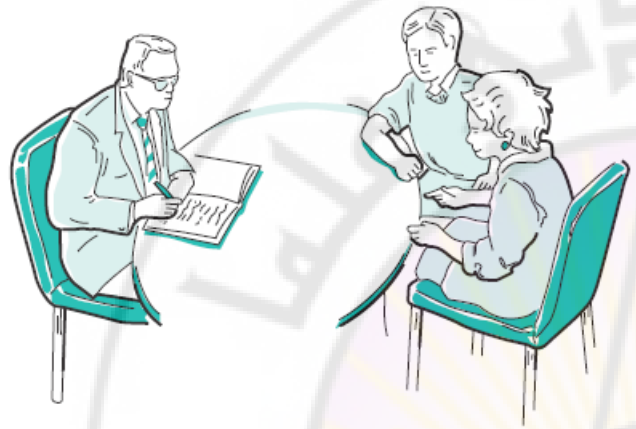
Pre-attack
Attack
Post-attack

WITNESS

The value of a competent witness's account is enormous in forming a diagnosis.

Arriving at a firm diagnosis in a patient who has suffered unwitnessed attacks is often much more difficult.

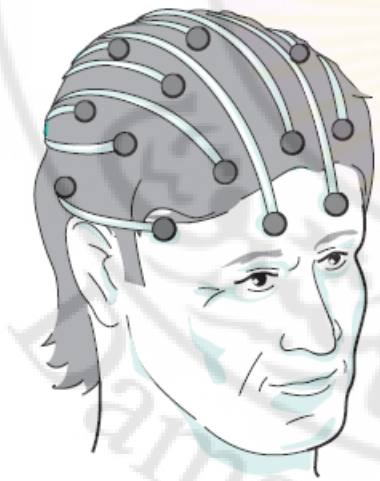

Unconsciousness
Blackouts



'First you tell me what happened, and then we will ask your husband for all the details too'

Often **no tests** necessary:

- adolescent with a typical vasovagal syncope
- elderly person on medication with demonstrable postural hypotension

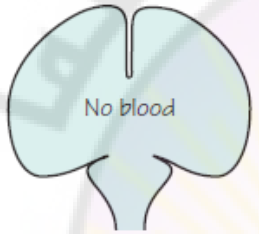


Standard EEG

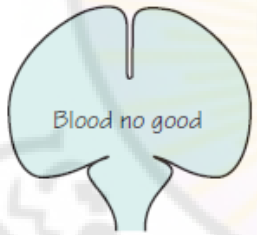
Ambulatory ECG

The common causes of blackouts

Generalized cerebral malfunction

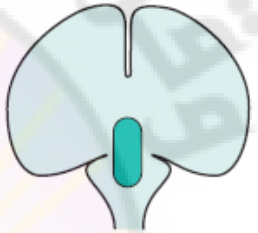


Vasovagal syncope
Postural hypotension
Hyperventilation
Cardiac dysrhythmia



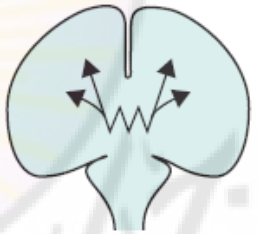
Hypoxia
Hypoglycaemia

Severe localized brainstem lesion



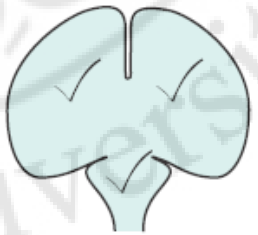
Transient ischaemic attacks in the vertebro-basilar circulation

Both generalized cerebral and brainstem lesion

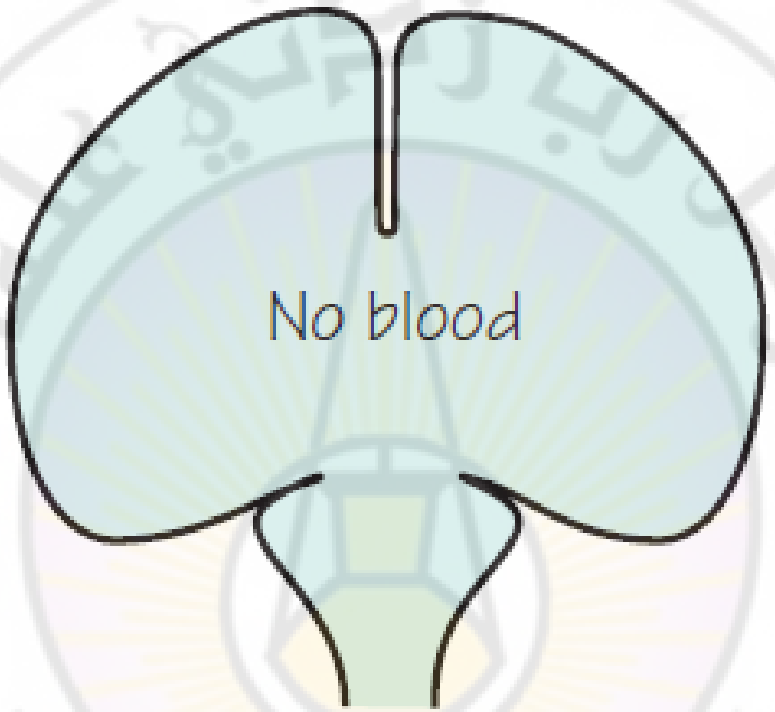


Primary generalized epilepsy

Neither generalized cerebral nor brainstem lesion



Psychologically mediated (hysterical) attacks



Vasovagal syncope
Postural hypotension
Hyperventilation
Cardiac dysrhythmia

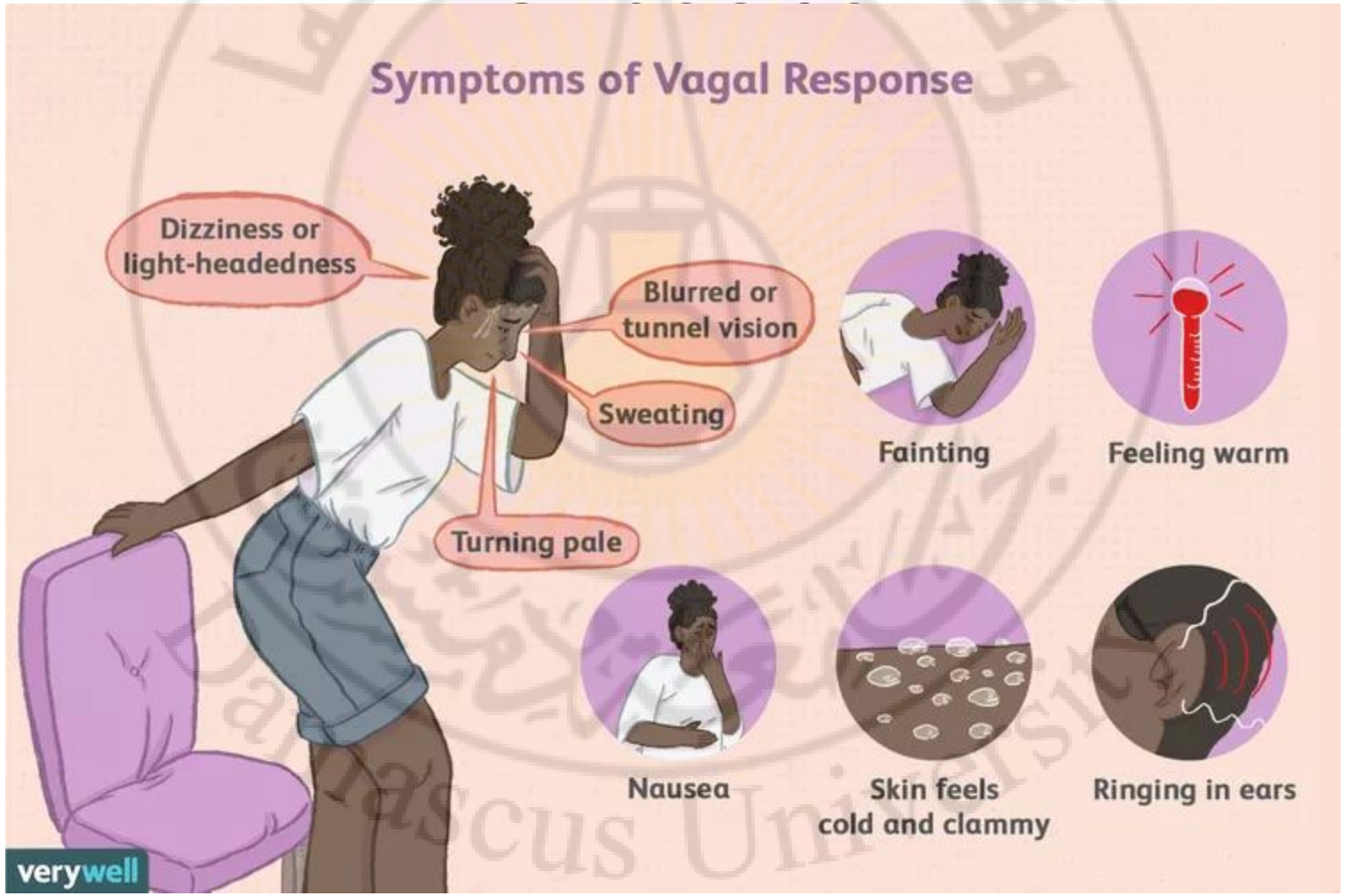
Syncope

Pre-attack:
nausea ,dizziness, sweating,…

Attack:
gradual, fall, pale, occasionally shivering, if prolonged may progress to GTC

Post-attack:
rapid return to consciousness when flat on floor

Vasovagal


Symptoms of Vagal Response
Dizziness or light-headedness
Blurred or tunnel vision
Sweating
Turning pale
Fainting
Feeling warm
Nausea
Skin feels cold and clammy
Ringing in ears
verywell

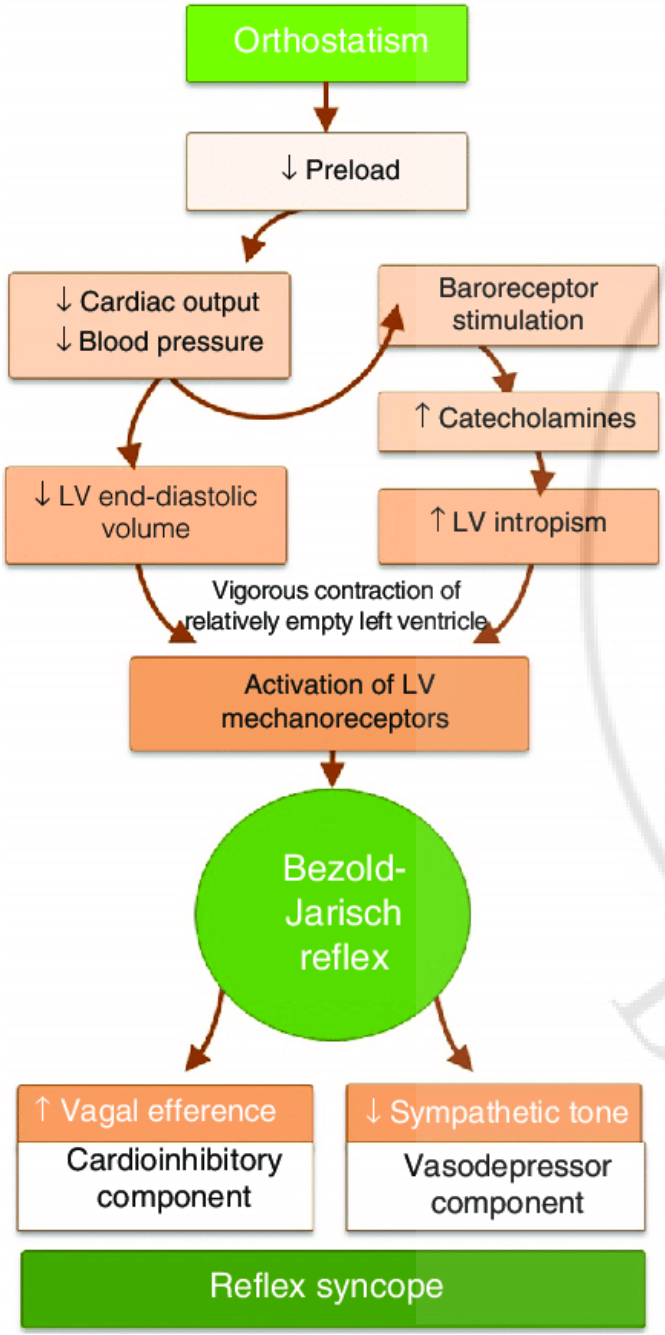
Syncope triggers

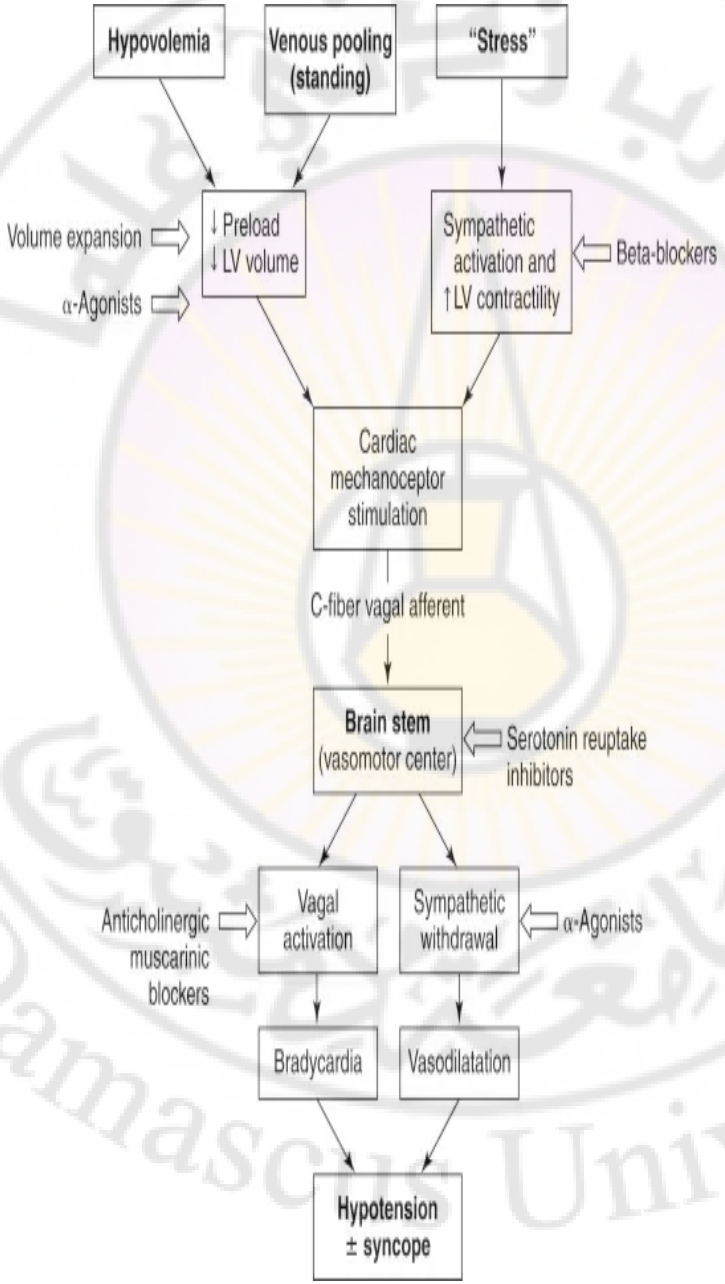
Defecation	Cough
Glossopharyngeal neuralgia	Postprandial
Orthostatic	Valsalva manouver
Oculovagal manouver	Sneezing
Venipuncture	Diving
Jacuzzi	Weight-lifting
Trumpet playing	Carotid sinus stimulation
Instrumentation (e.g. small surgical procedures)	Staying inside too ample or crowded places
Drugs	

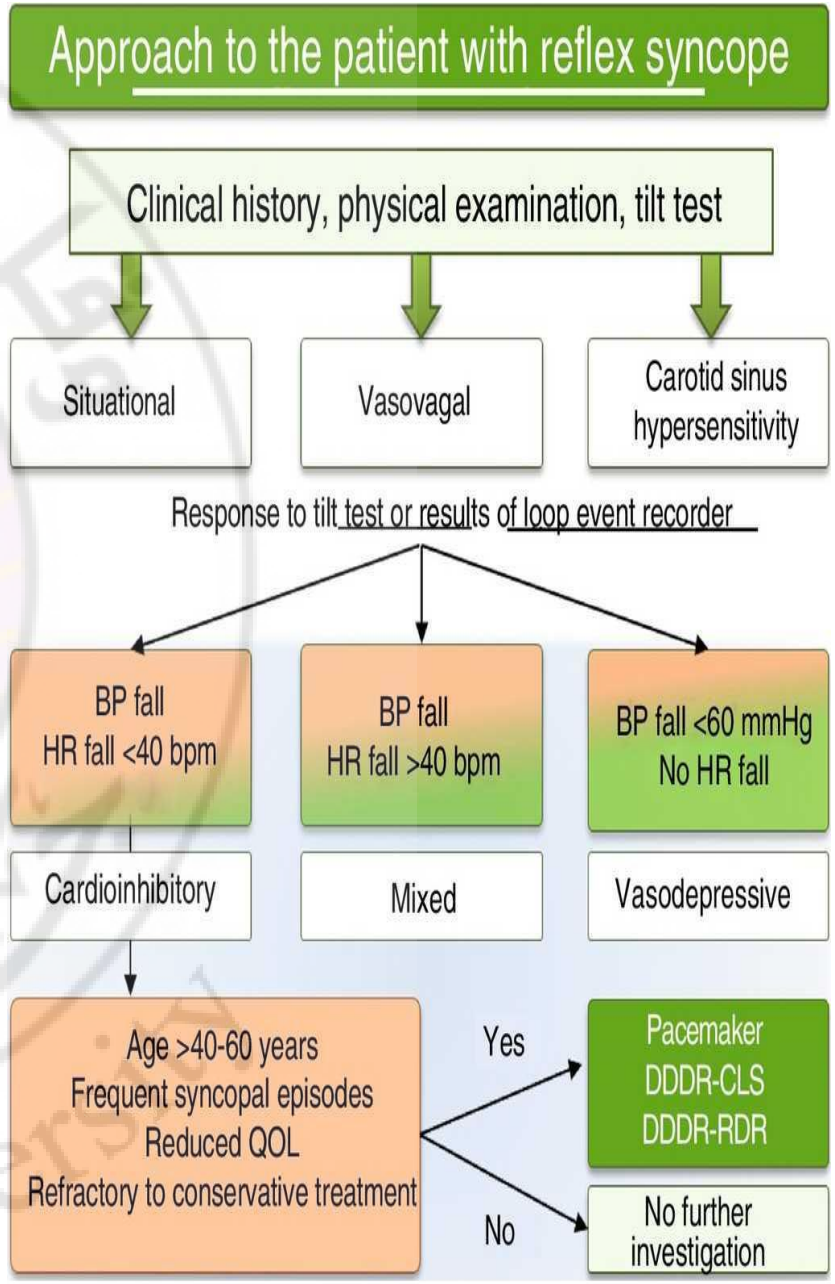
*modified from Landau[21].

Vasovagal

Short period (30–120 seconds)





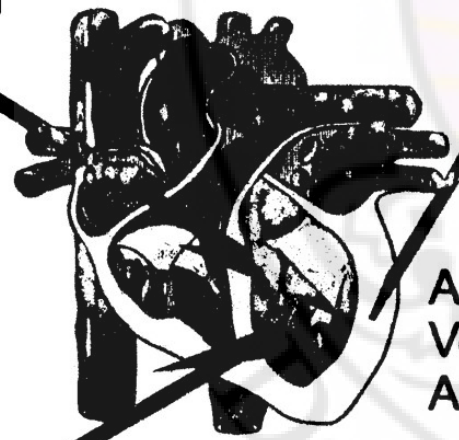


Rev Port Cardiol. 2019;38:661-73

Normal increased sympathetic tone replaced by increased vagal tone

BRAINSTEM

Exaggerated Sympathetic Activation



Activation Ventricular Afferents

Circulating Hypovolemia

Sympathetic Withdrawal

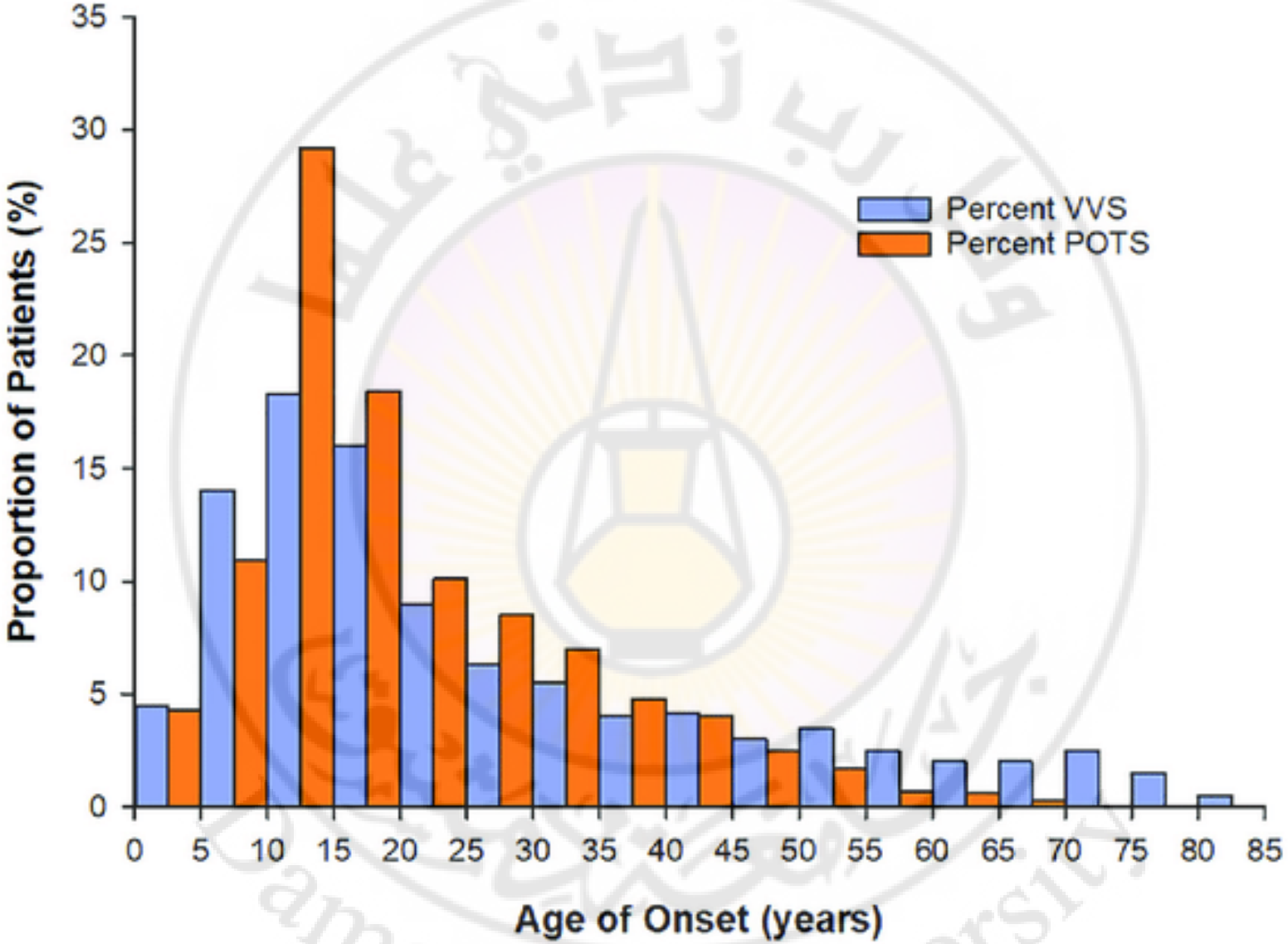
Vasodilation

Hypotension

Vagal Tone

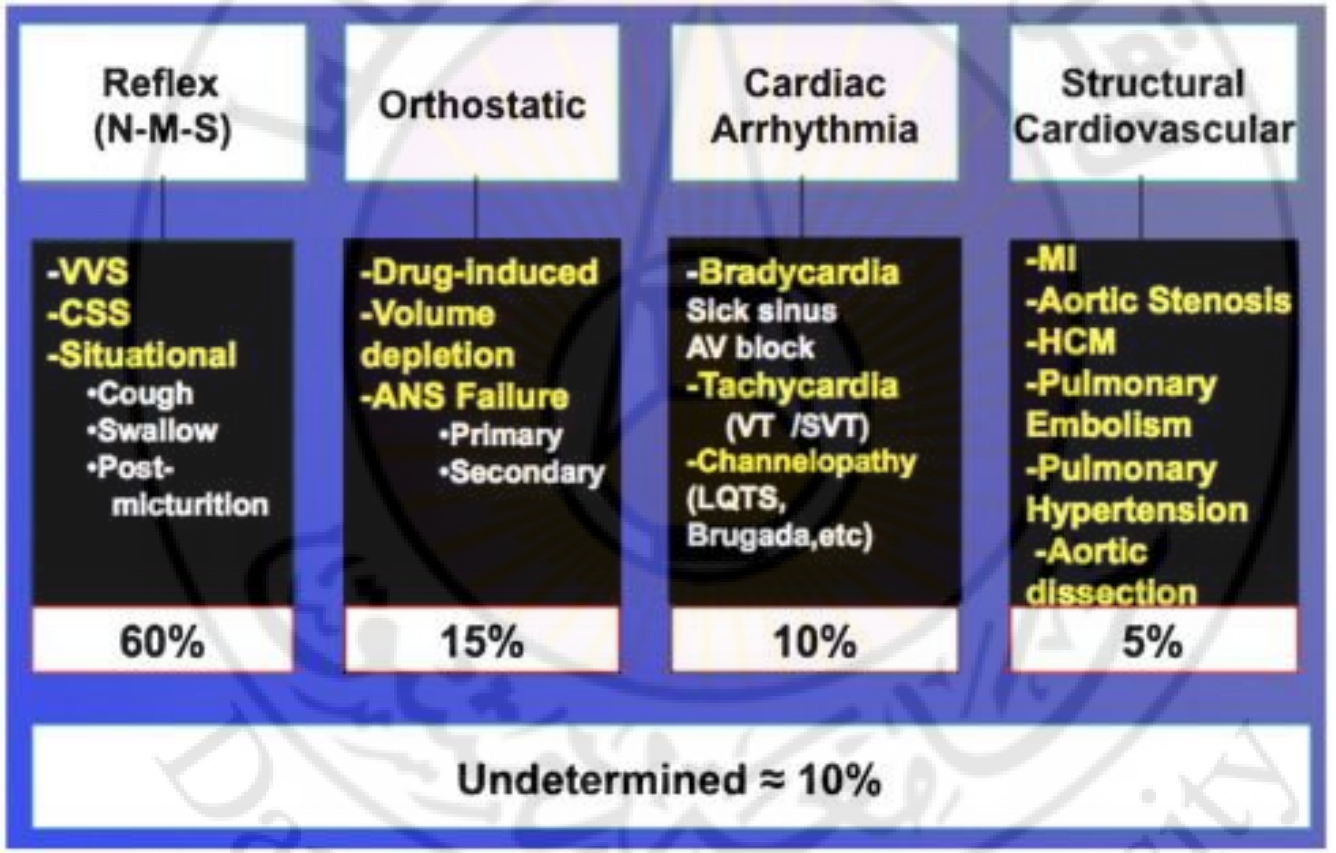
Bradycardia

Syncope



They are more common in teenage and young adult life

Syncope classification



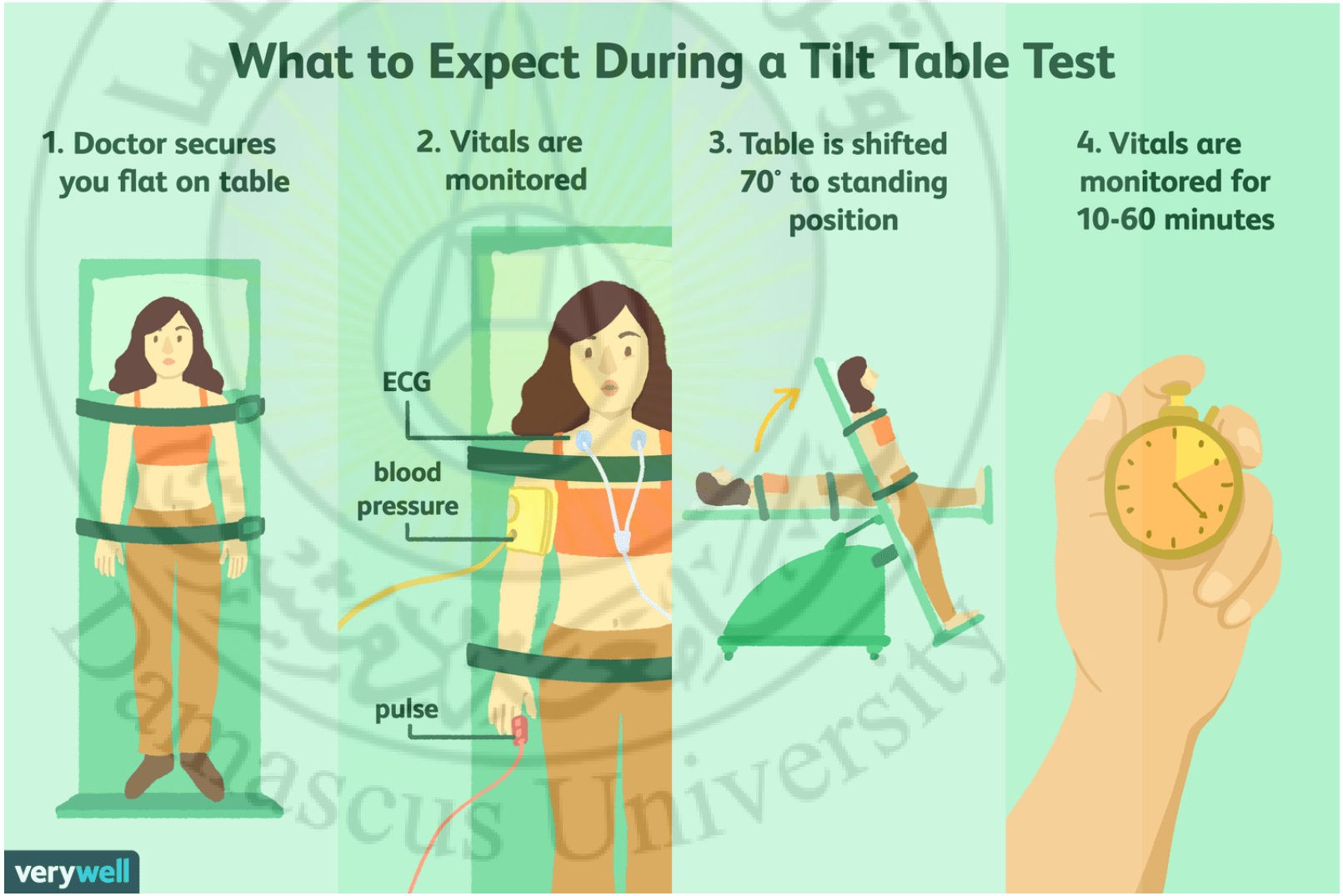
Without any warning

Syncope due to to aortic stenosis or complete heart heart block

Syncope classification

The Normal Response to a Tilt-Table Test

A normal tilt response includes a mild increase in diastolic pressure by 5–10 mmHg, a mild decrease in systolic blood pressure of 5–10 mmHg, and an increase in heart rate of about 10–20 bpm. A transient drop in blood pressure with reflex tachycardia within the first few minutes of tilt is common in healthy adolescents during tilt test



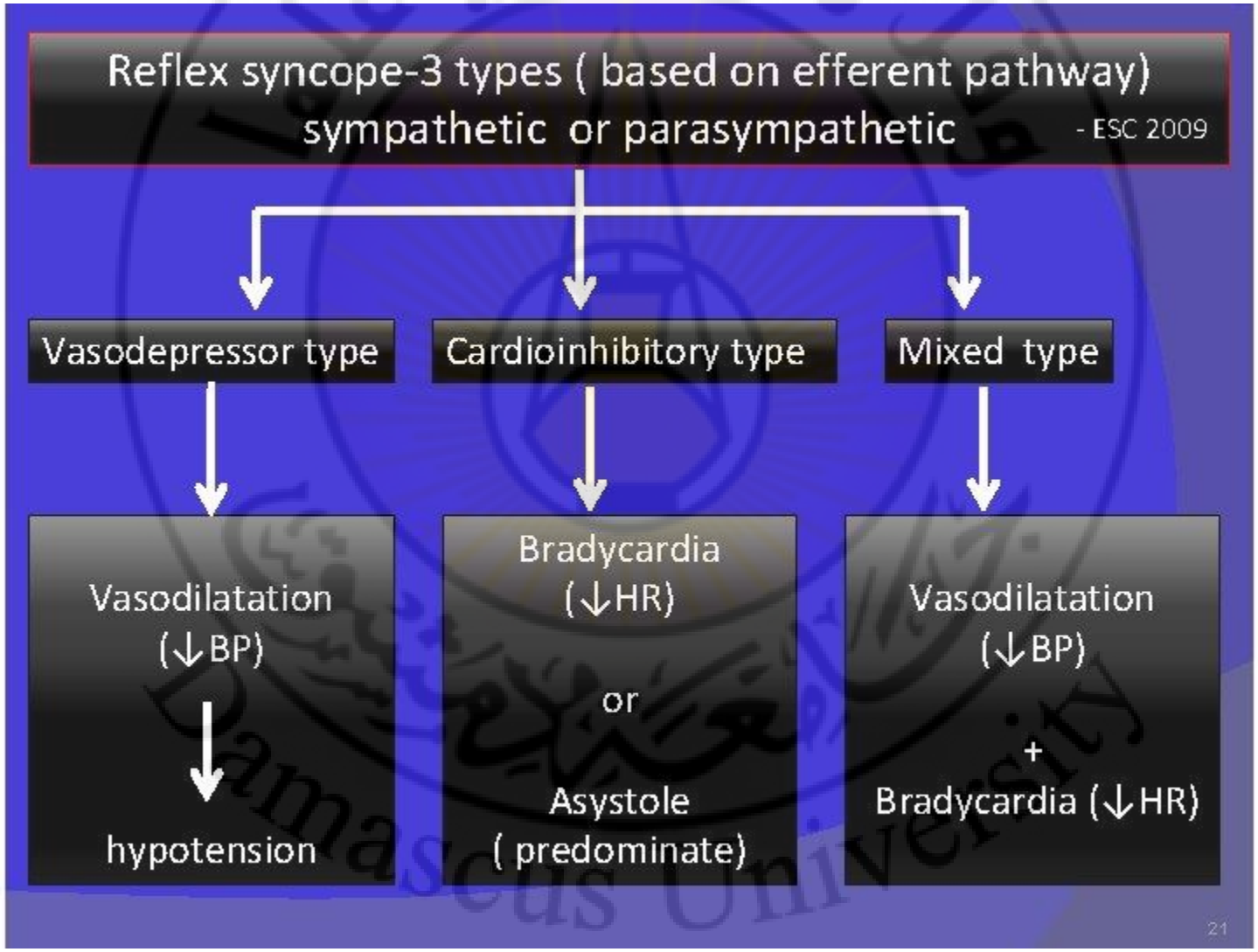
Syncope classification

Tilt Table Testing

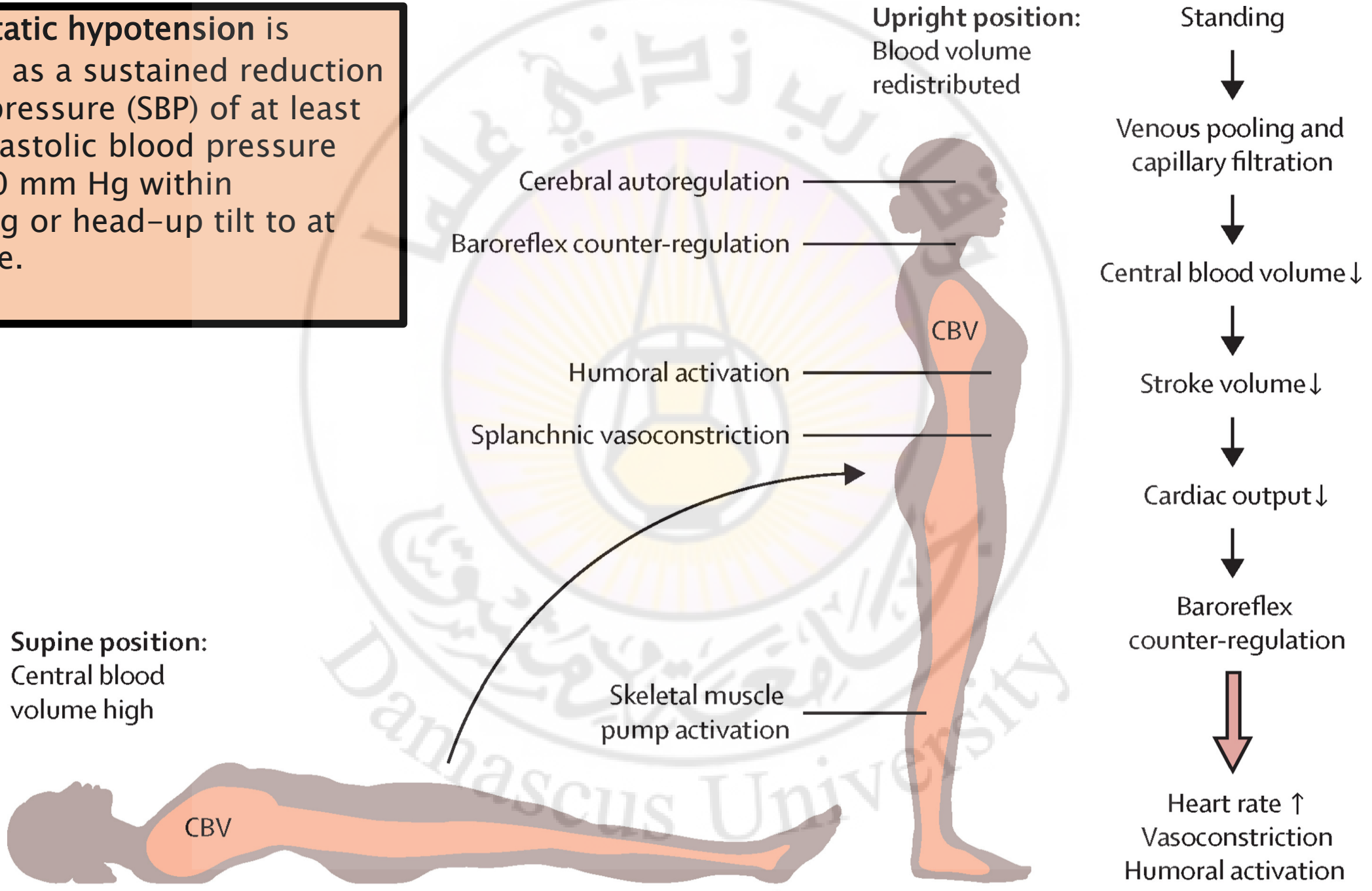
	Orthostatic Hypotension	Postural Tachycardia	Reflex Syncope
Definition	Gradual sustained ↓ sBP>20 dBP>10 ≤3′	↑HR>30 in 10′ no ↓ BP	Sudden ↓ BP ± HR
BP / HR Pattern			
Physiology	Arterial denervation impacts ***diastole***	Venous return impacts ***systole***	Brainstem ***threshold***
CV reflexes	Usually abnormal	Usually normal	Usually nl
Associated Dysauton.	Structural Poor prognosis	Functional Good Prognosis	Functional

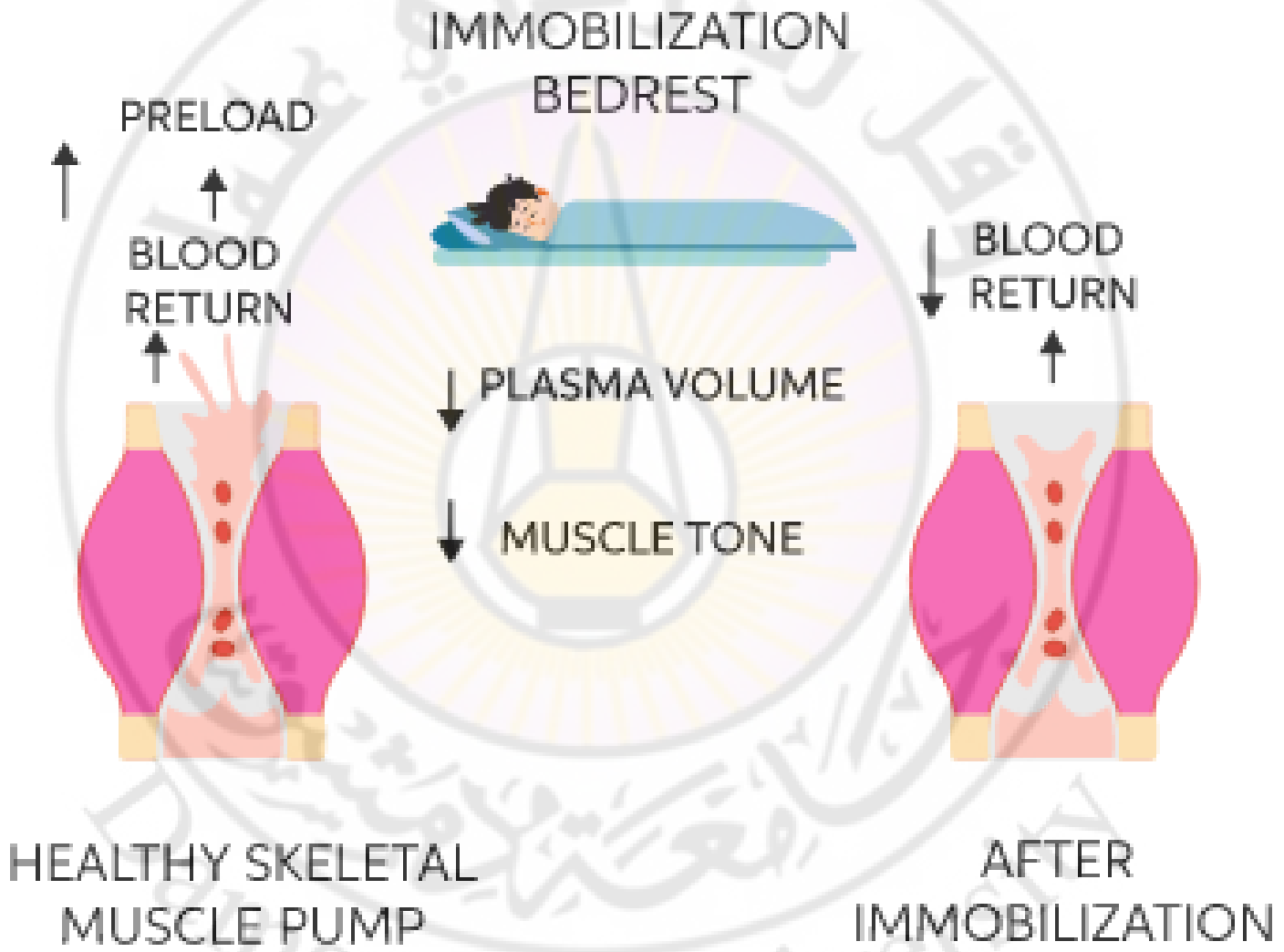
blood pressure (*black line*) and heart rate (*red line*)

Syncope classification



Orthostatic hypotension is defined as a sustained reduction blood pressure (SBP) of at least or of diastolic blood pressure least 10 mm Hg within standing or head-up tilt to at tilt table.




IMMOBILIZATION
BEDREST
PRELOAD
BLOOD
RETURN
PLASMA VOLUME
MUSCLE TONE
BLOOD
RETURN
HEALTHY SKELETAL
MUSCLE PUMP
AFTER
IMMOBILIZATION

SPH evaluation procedure

Measure twice
- Blood pressure
- Heart rate

Measure twice
- Blood pressure
- Heart rate

Measure twice
- Blood pressure
- Heart rate

≥20 mmHg ↓ in SBP
and/or
≥10 mmHg ↓ in DBP

→ Seated PH

Postural hypotension

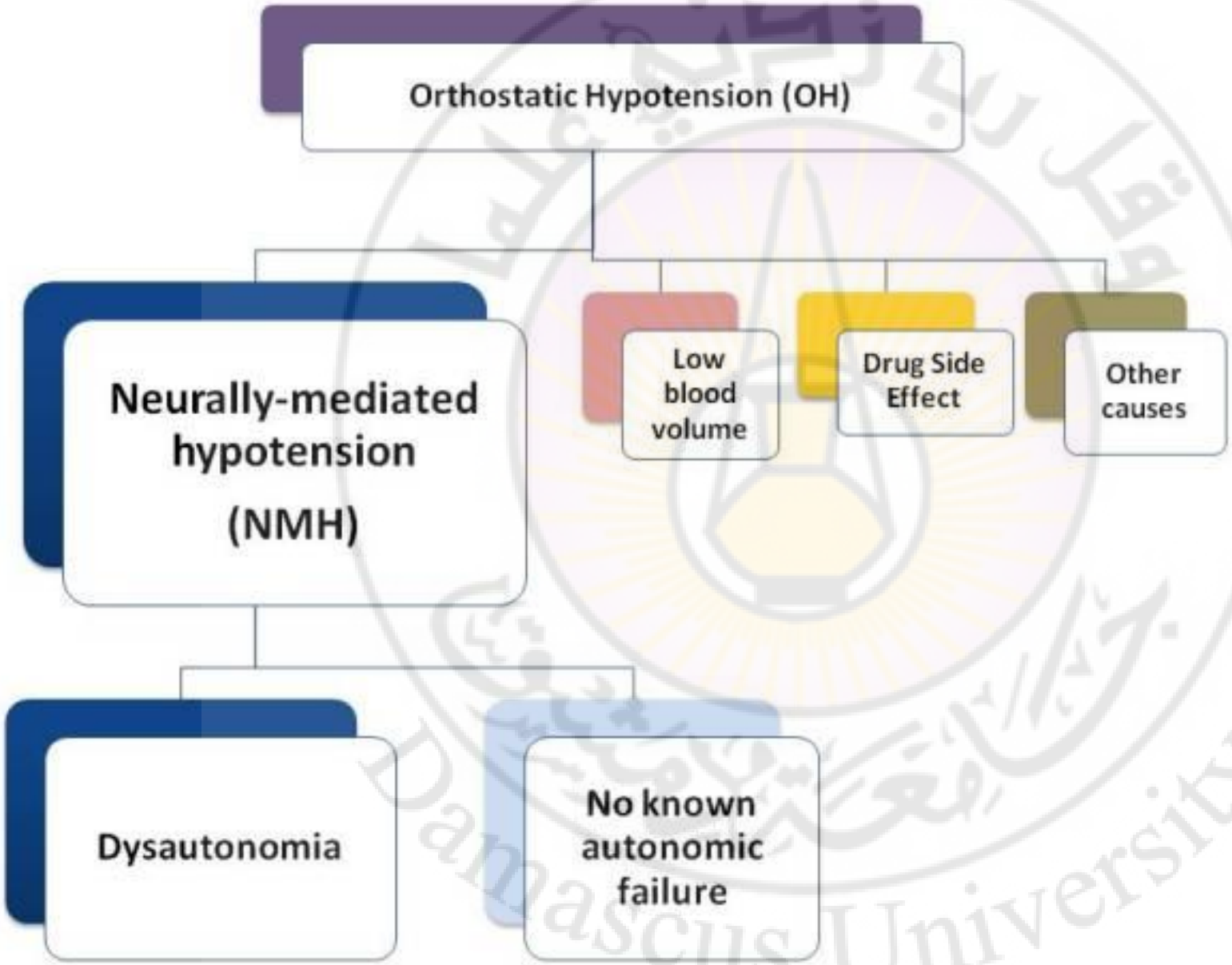
The drop in blood pressure may be sudden (vasovagal orthostatic hypotension), within 3 minutes (classic orthostatic hypotension) or gradual (delayed orthostatic hypotension)

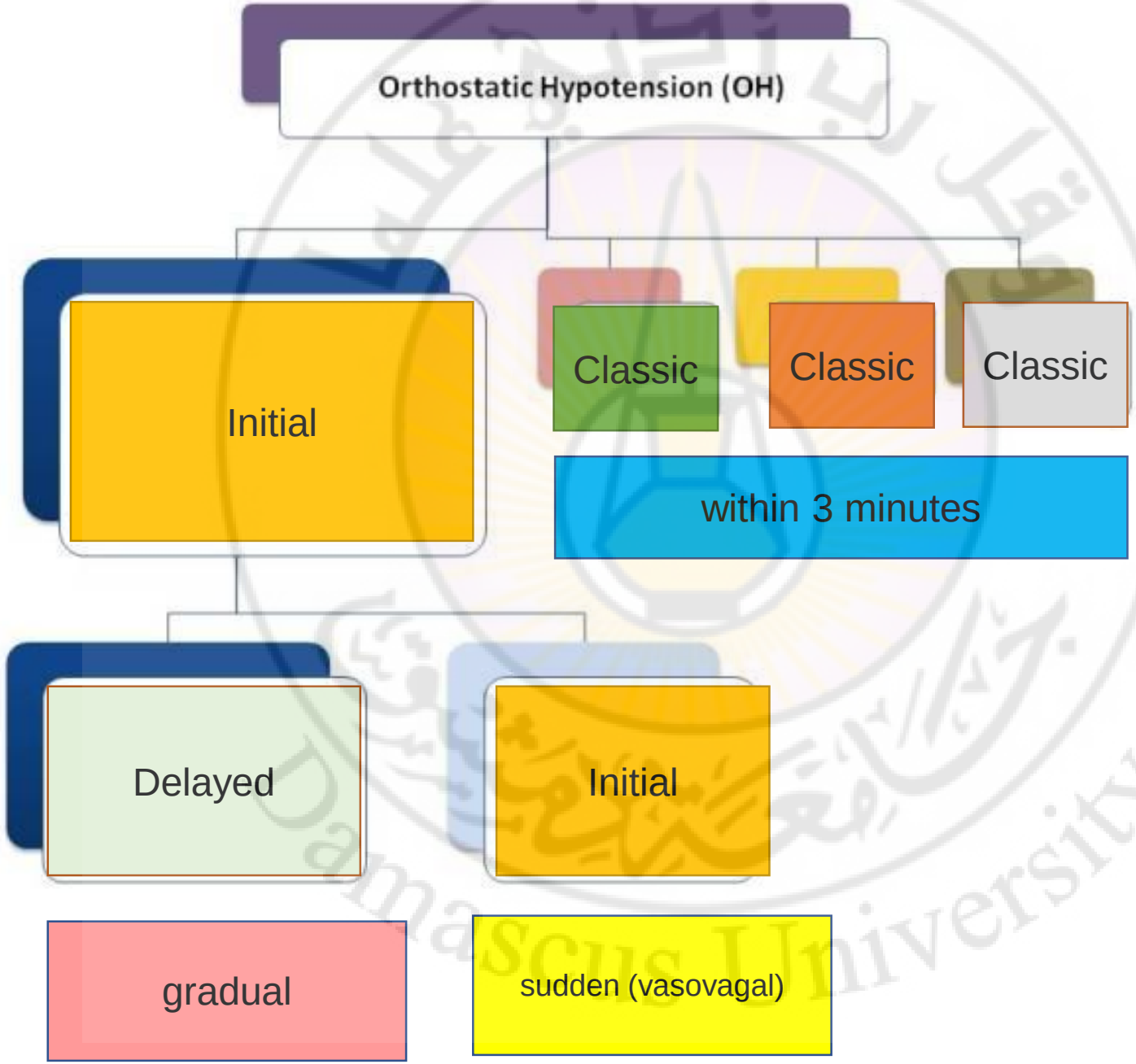
Orthostatic hypotension can be subcategorized into three groups – initial, classic, and delayed.

Initial orthostatic hypotension is frequently characterized by a systolic blood pressure decrease of ≥40 mmHg or diastolic blood pressure decrease of ≥20 mmHg within 15 seconds of standing. Blood pressure then spontaneously and rapidly returns to normal, so the period of hypotension and symptoms is short (<30 s). Only continuous beat-to-beat BP measurement during an active standing-up maneuver can document this condition.

Classic orthostatic hypotension is frequently characterized by a systolic blood pressure decrease of ≥20 mmHg or diastolic blood pressure decrease of ≥10 mmHg between 30 seconds and 3 min of standing.

Delayed orthostatic hypotension is frequently characterized by a sustained systolic blood pressure decrease of ≥20 mm Hg or a sustained diastolic blood pressure decrease ≥of 10 mm Hg beyond 3 minutes of standing or upright tilt table testing


Orthostatic Hypotension (OH)
Neurally-mediated hypotension (NMH)
Low blood volume
Drug Side Effect
Other causes
Dysautonomia
No known autonomic failure


Orthostatic Hypotension (OH)
Initial
Classic
Classic
Classic
within 3 minutes
Delayed
Initial
gradual
sudden (vasovagal)

Digitalis
Foxglove

Hyperventilation


unemployment
chronic pain
work stress
new baby
illness
fear
STRESS
grief
new job
bullying
divorce
health problems
increase of symptoms
hyperventilation
THE HYPERVENTILATION CYCLE
feel unwell
more hyperventilation
anxiety

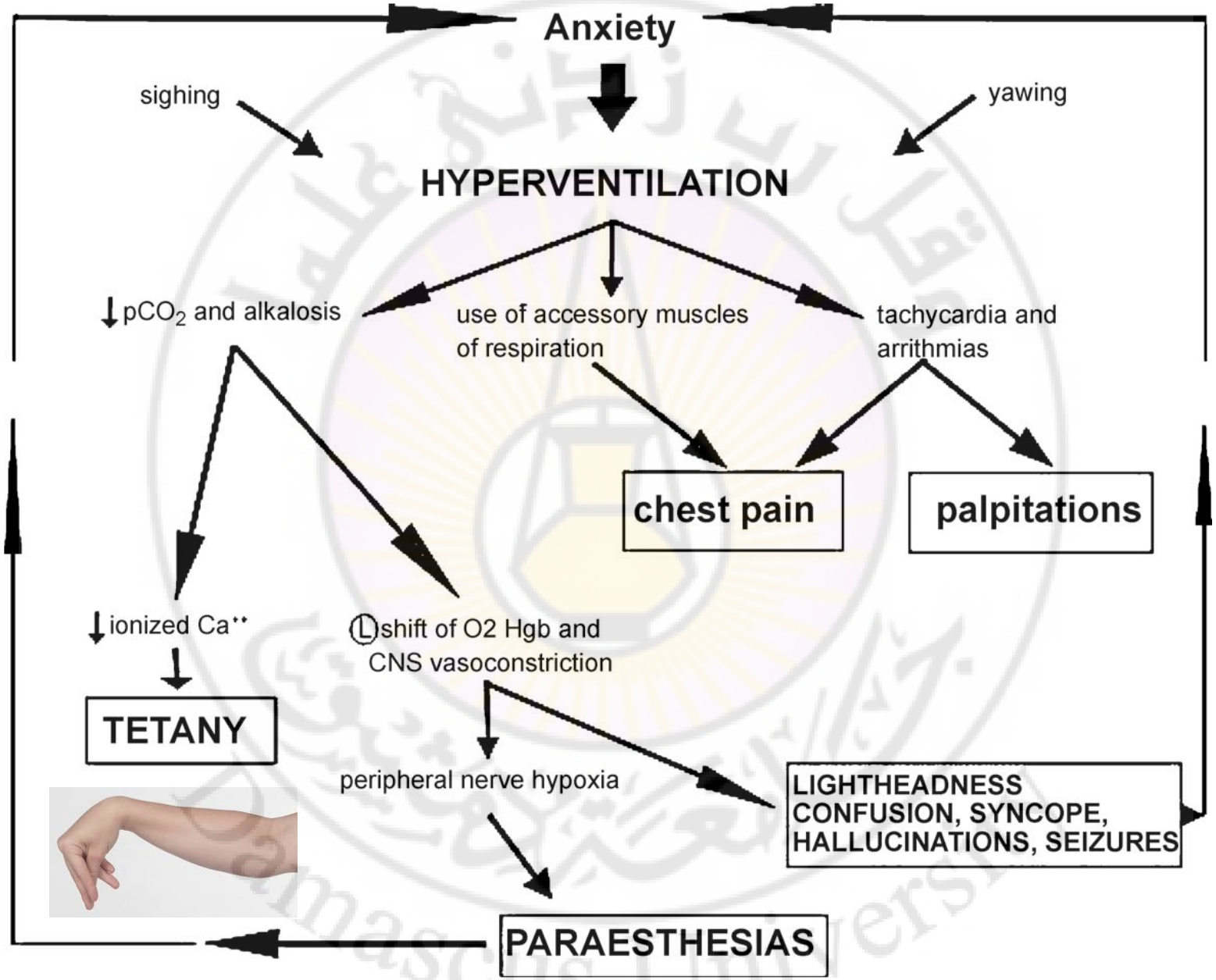
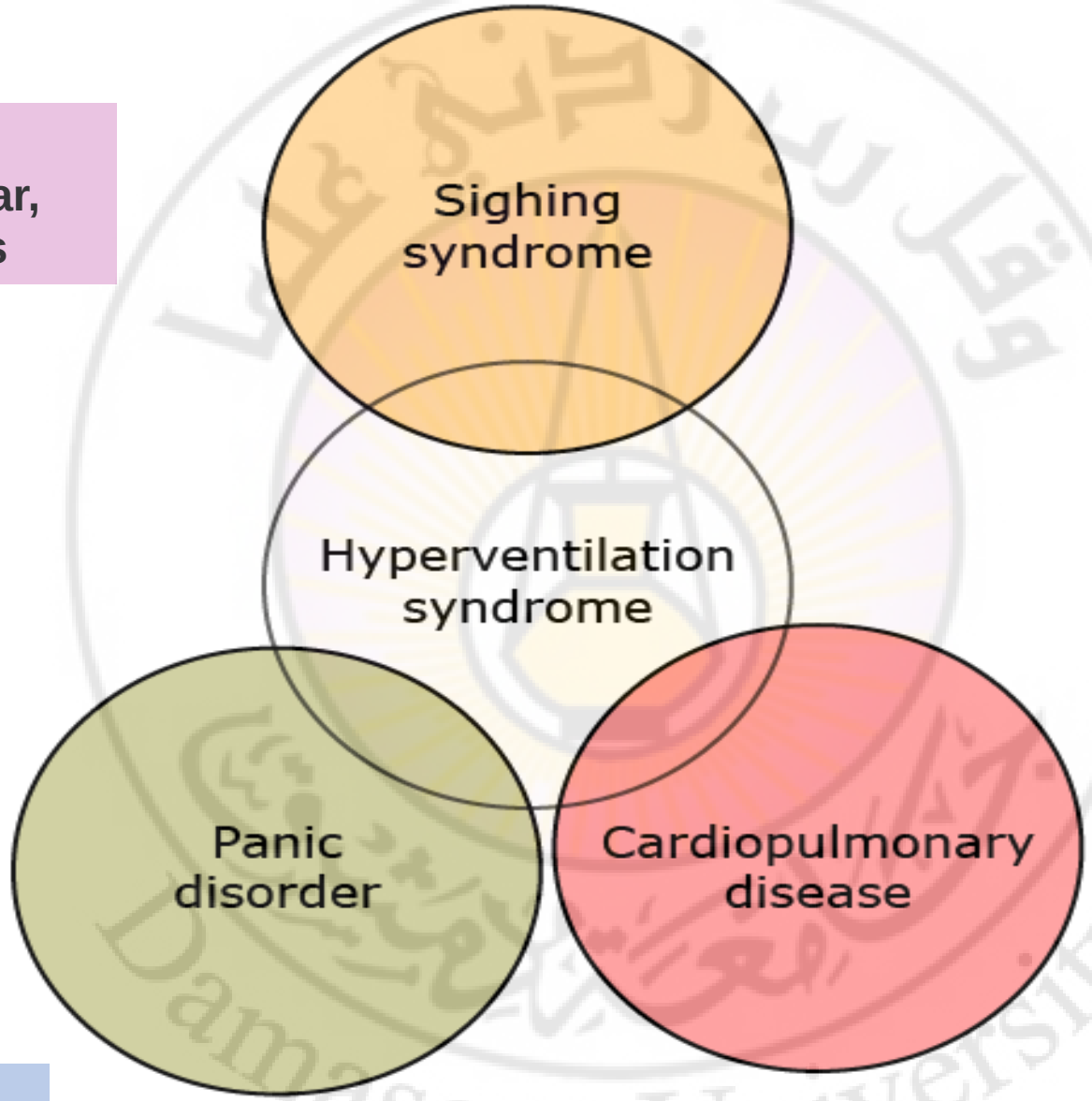
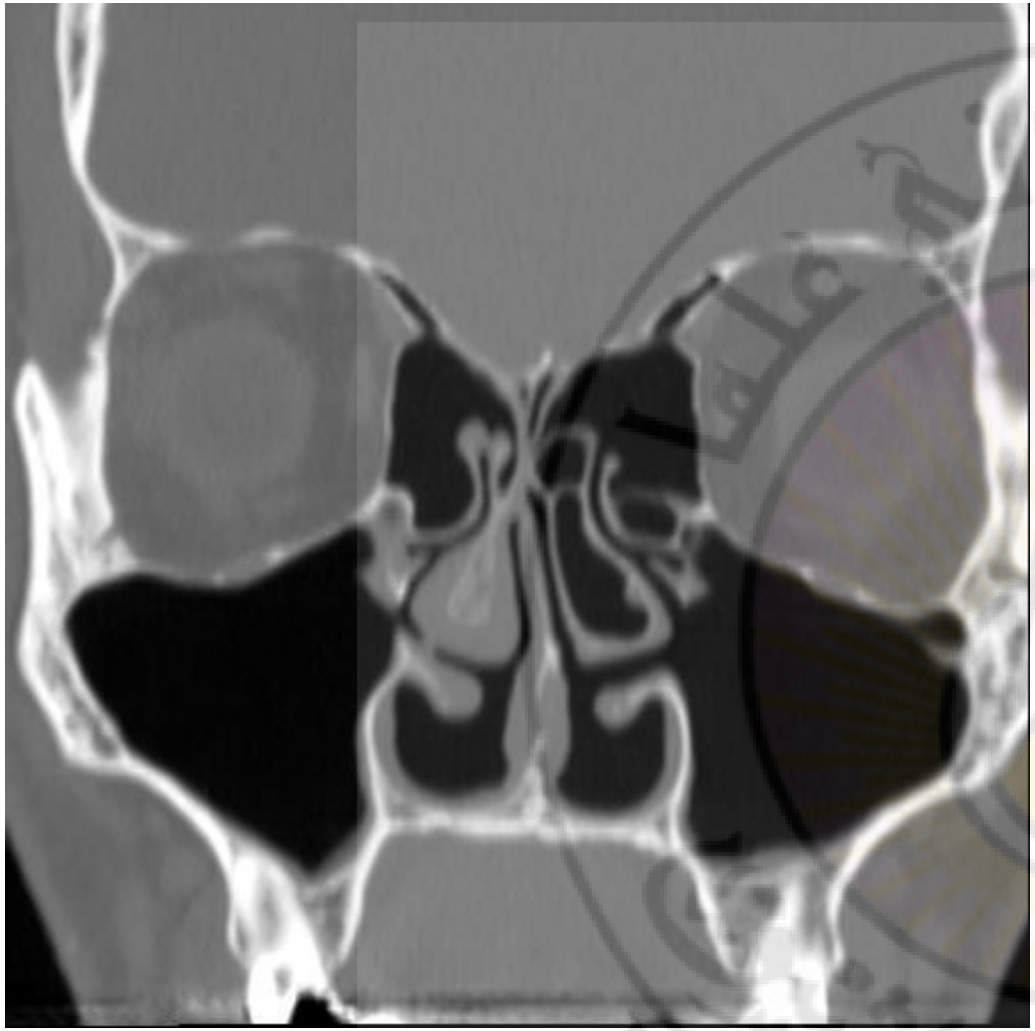


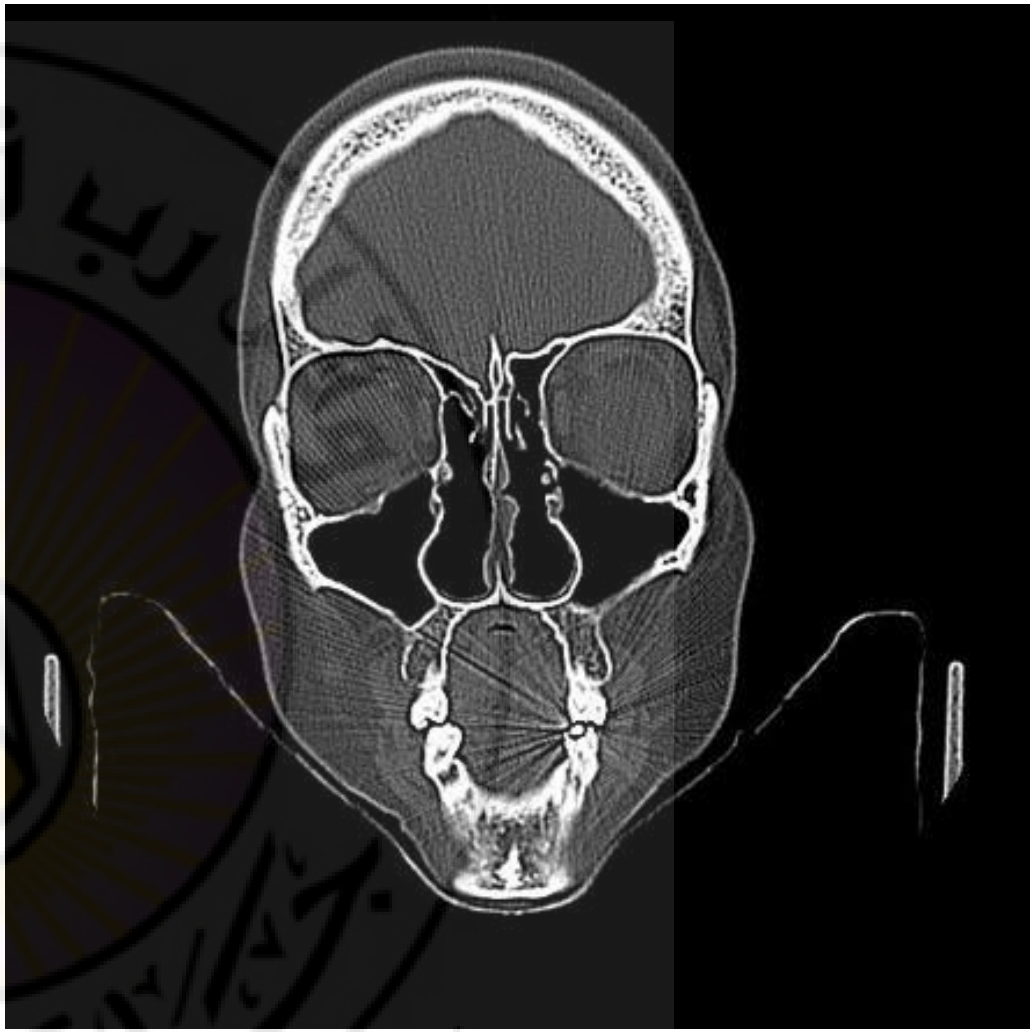
Figure 1. Pathofysiologic mechanism of hyperventilation.(adapted from Herman *et al.*)[17]

Negative emotional states — such as fear, anxiety and sadness

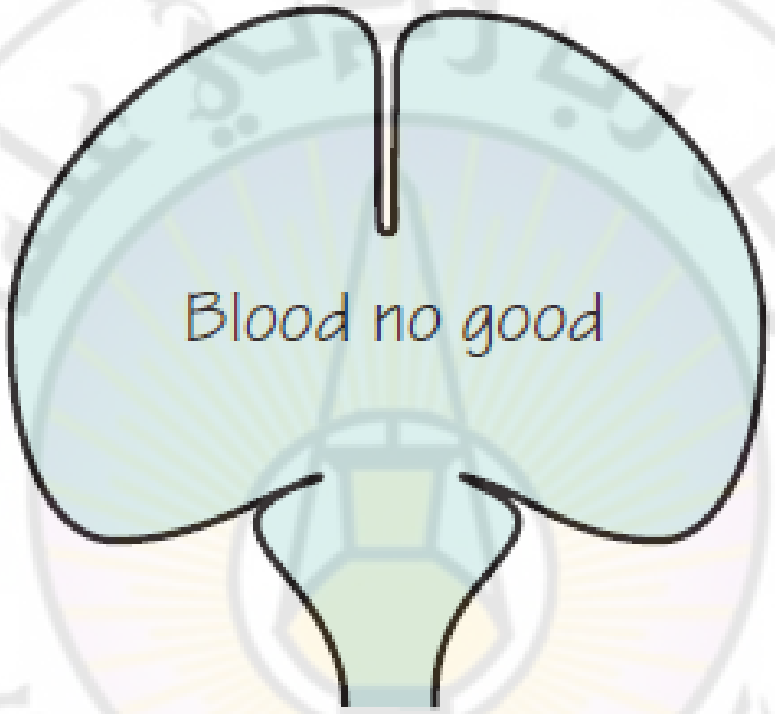


A feeling of sudden and intense anxiety

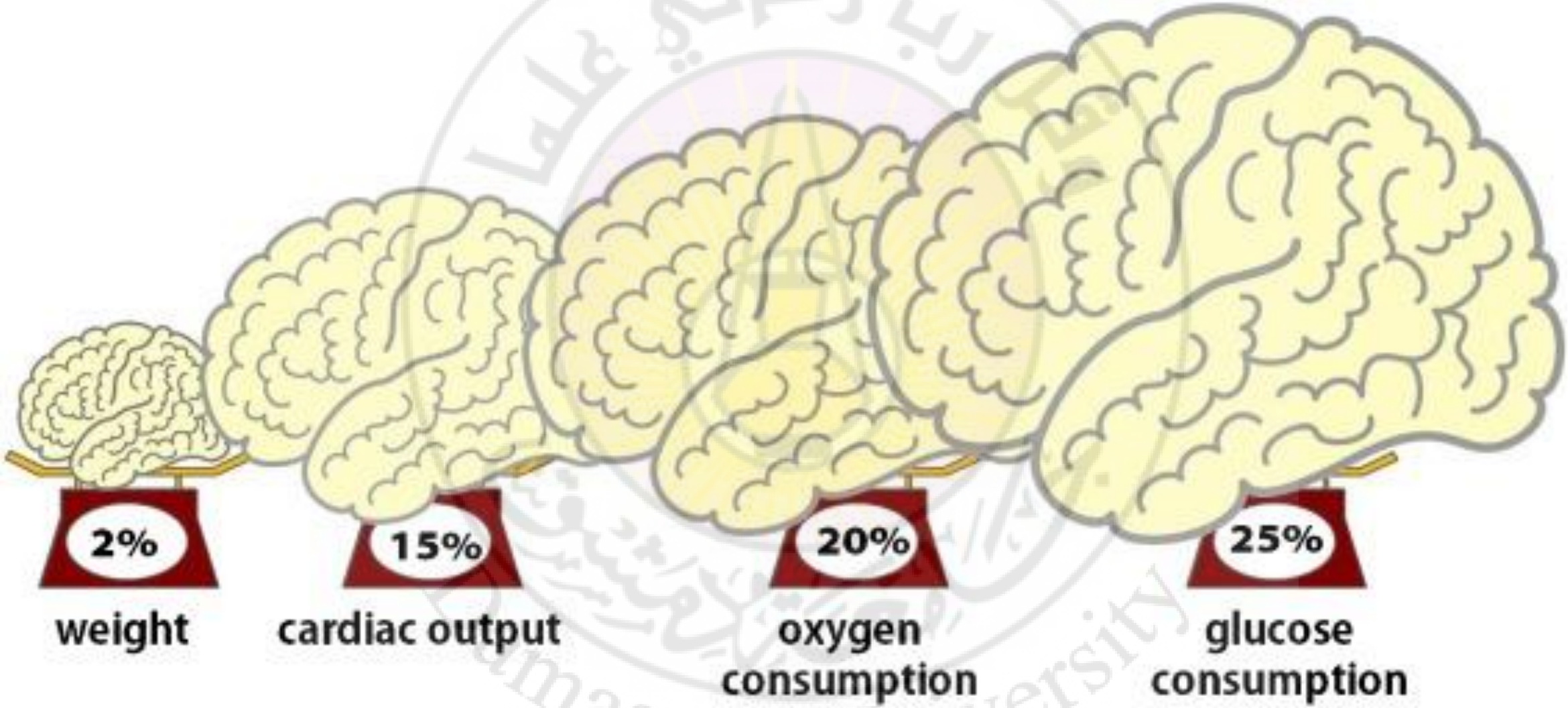


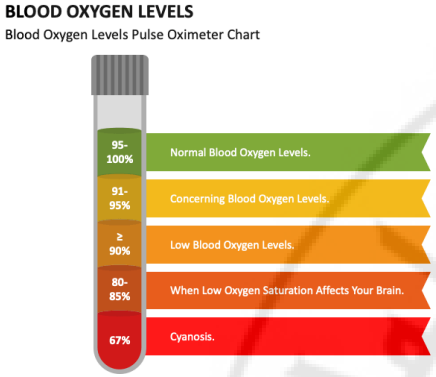


A study, found that 77% of patients with empty nose syndrome have hyperventilation syndrome. Empty nose syndrome can appear in people having done nose surgery like cauterization, turbinectomy, turbinoplasty, etc



Hypoxia
Hypoglycaemia


2%
15%
20%
25%
weight
cardiac output
oxygen consumption
glucose consumption



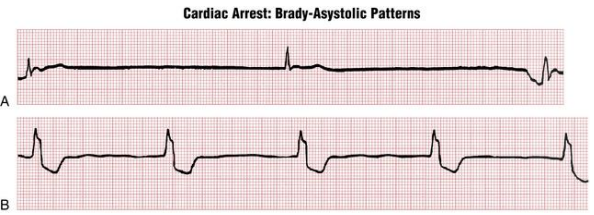
Hypoxia

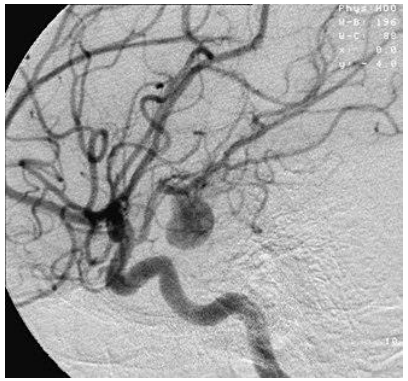
Diffuse cerebral hypoxia – A mild to moderate impairment of brain function due to low oxygen levels in the blood

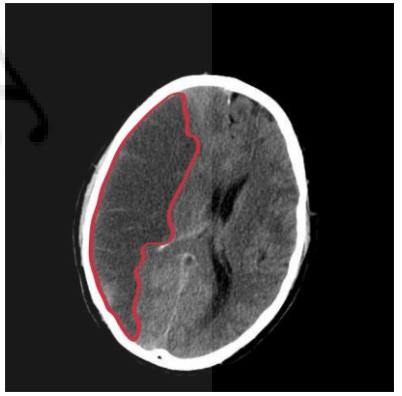
Global cerebral ischemia – A complete stoppage of blood flow to the brain

Focal cerebral ischemia – A stroke occurring in a localized area that can either be acute or transient

Cerebral infarction – A "stroke", caused by complete oxygen deprivation





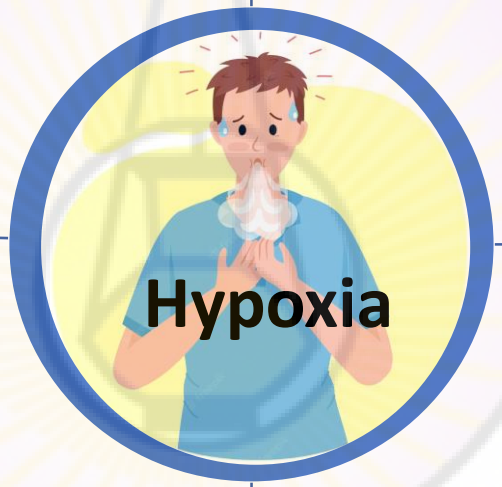


Hypoxic hypoxia

Limited oxygen in the environment causes reduced brain function. Divers, aviator,mountai climbers

Hypemic hypoxia

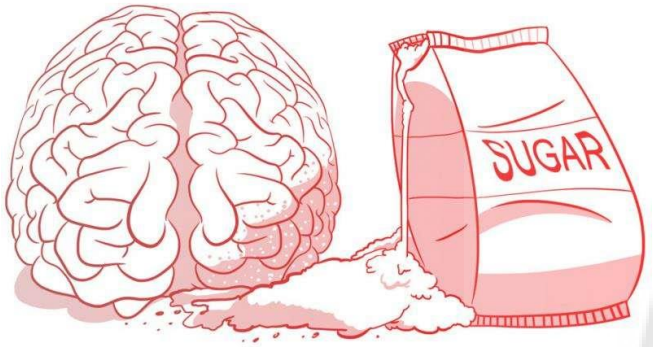
Reduced brain function is caused by inadequate oxygen in the blood despite adequate environmental oxygen. Anemia and carbon monoxide poisoning



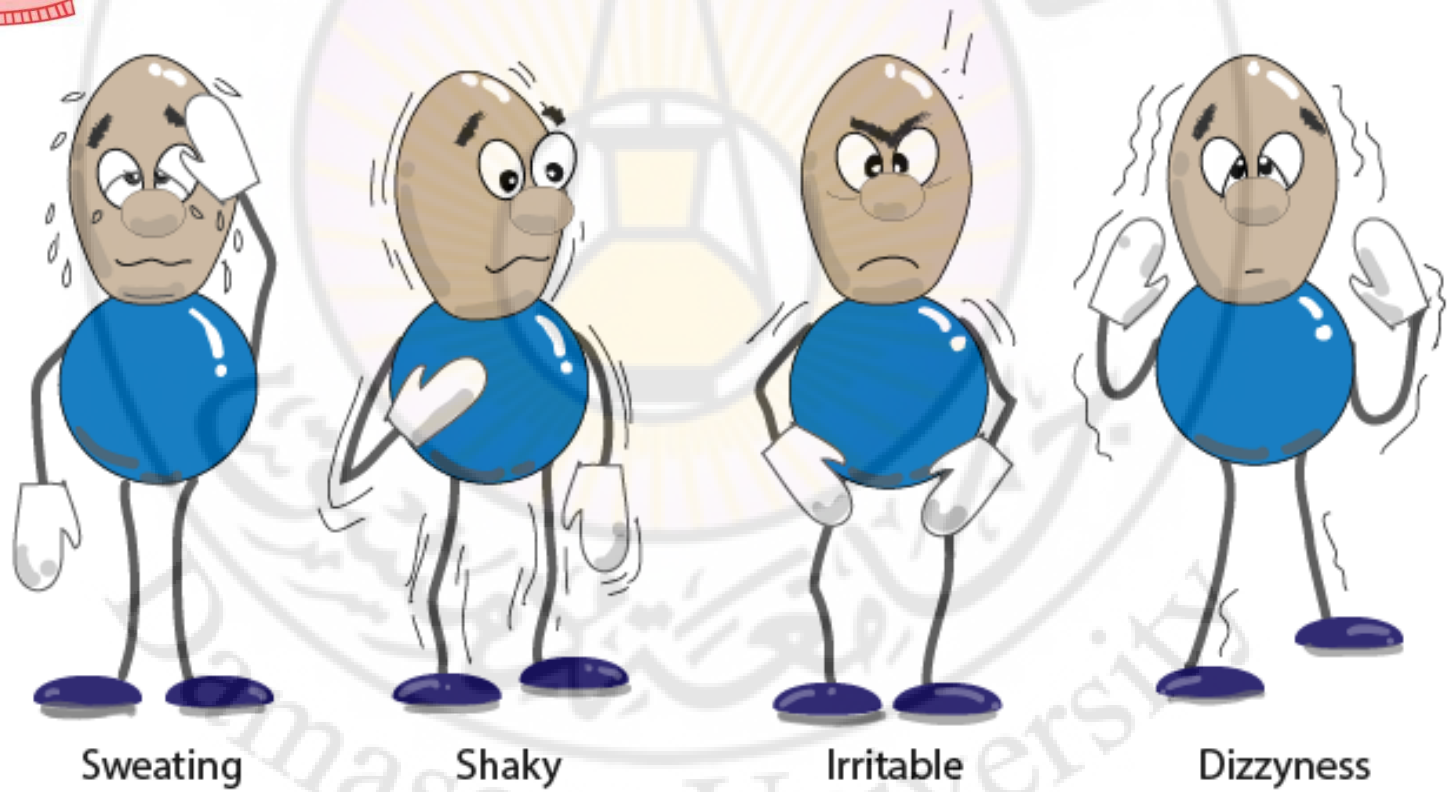
Histotoxic hypoxia

Oxygen is present in brain tissue but cannot be metabolized by the brain tissue. (Cyanide poisoning)

Ischemic hypoxia (or "stagnant hypoxia") – Reduced brain oxygen is caused by inadequate blood flow to the brain. Stroke, shock, cardiac arrest and heart attack may cause stagnant hypoxia

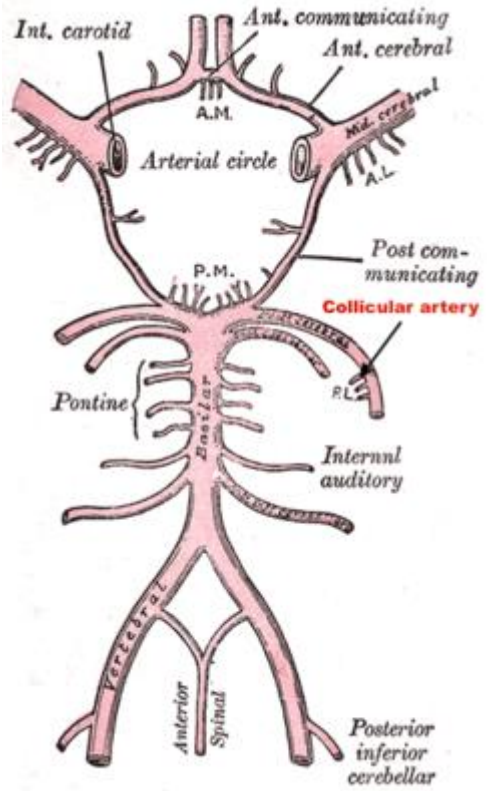


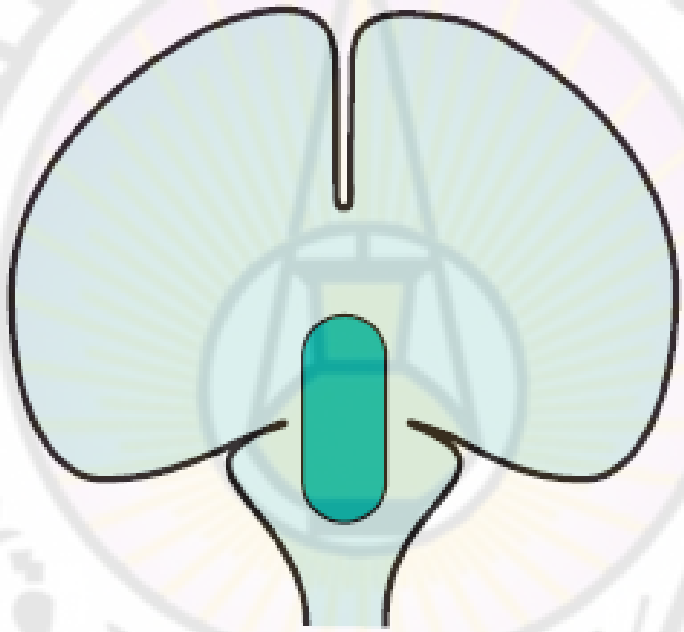
Hypoglycaemia



Hypoglycaemia

Vertebro-basilar transient ischaemic attacks





The patient is middle-aged or elderly

Symptoms of vertebrobasilar transient ischemic attacks are complex!

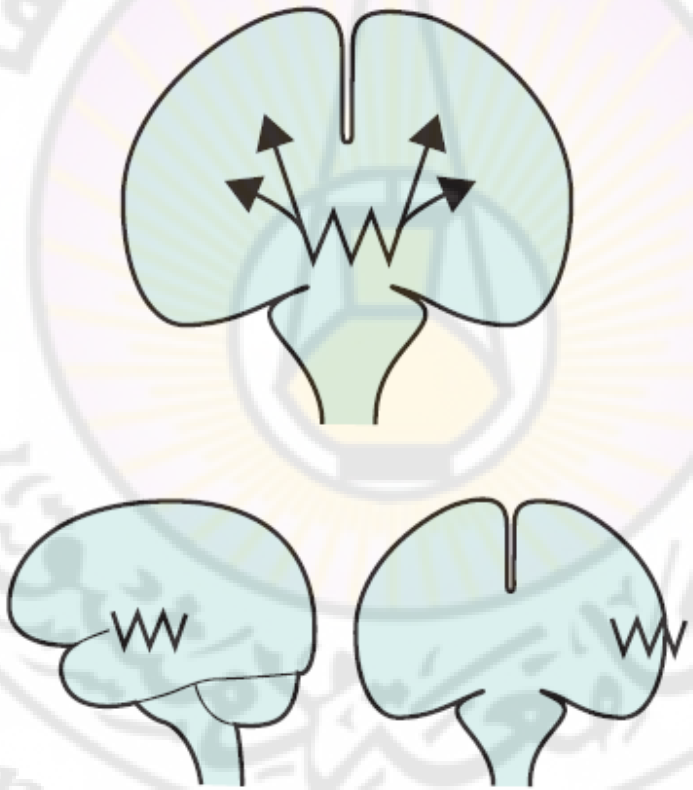
- Unilateral or bilateral motor or sensory symptoms involving the face or limbs and unilateral or bilateral visual field defects
  - Vertigo
  - Diplopia
  - Dysarthria, dyphagia
  - loss of balance
  - isolated sensory symptoms
- may be considered as transient ischemic attacks when occurring in combined fashion (simultaneously or successively)

  (Albucher et al 2005)

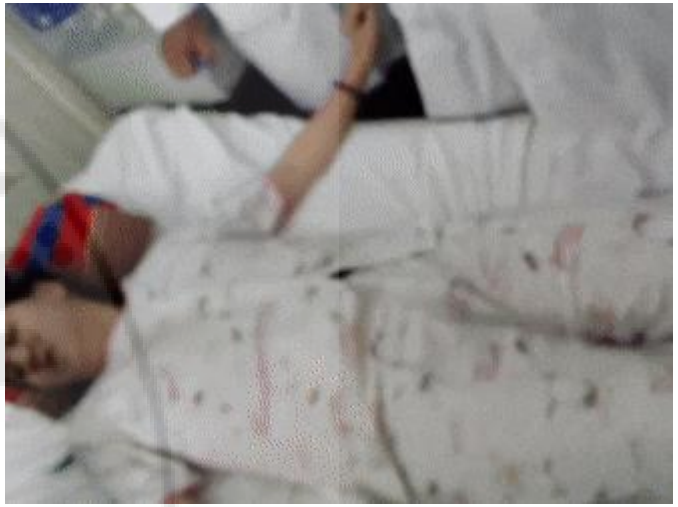
Table 2. Signs and Symptoms of Basilar-Artery Occlusion.

Corticospinal
Limb weakness (often bilateral)
Limb hyperreflexia
Extensor plantar response
Corticobulbar
Facial weakness
Dysarthria
Dysphagia
Increased gag reflex
Oculomotor
Diplopia
Gaze palsies
Nystagmus
Internuclear ophthalmoplegia
Reticular activating system
Reduced consciousness

Epilepsy



Seizures



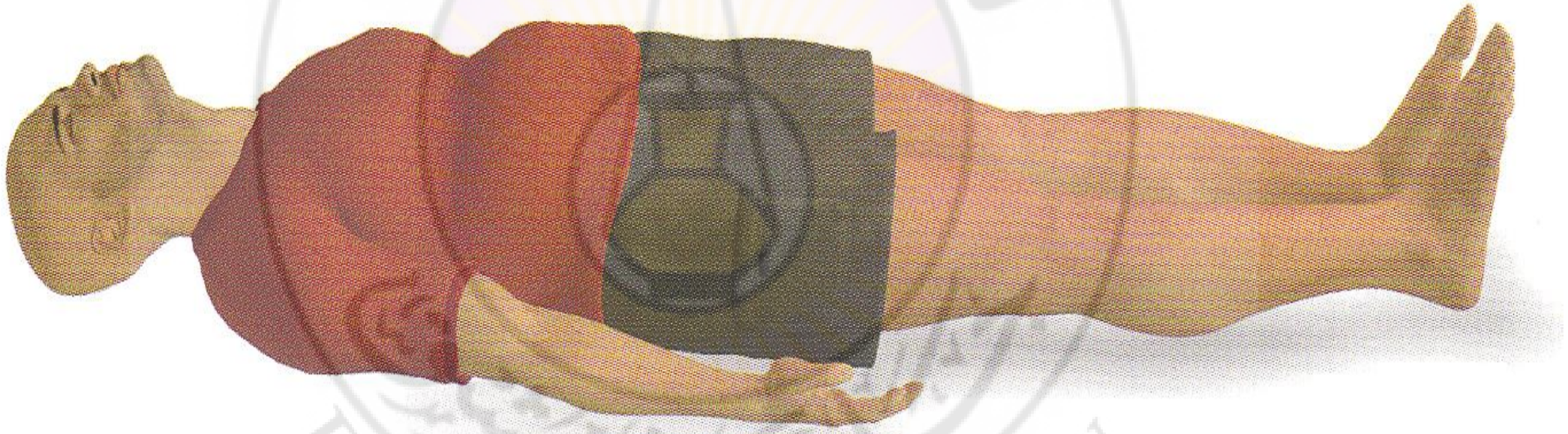
Pre-attack:
no warning or aura

Attack:
tonic phase the respiration ceases, cyanosis
Clonic phase jerking all four limbs
tongue biting+/- incontinence

Post attack:
deep sleep
diffuse bodily aching or stiffness

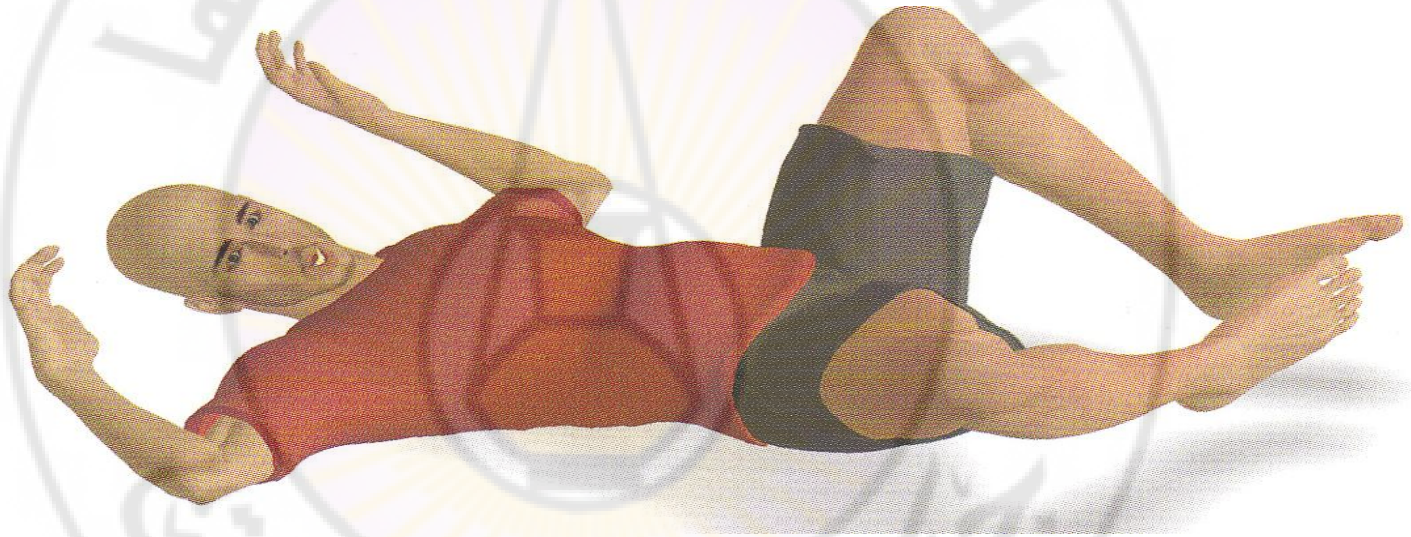
Tonic Clonic Seizure

Pre-Ictal Stage



Pre-ictal: In this example the patient is relaxing in bed and eyes are closed

Tonic Stage: Initial Stage In Flexion



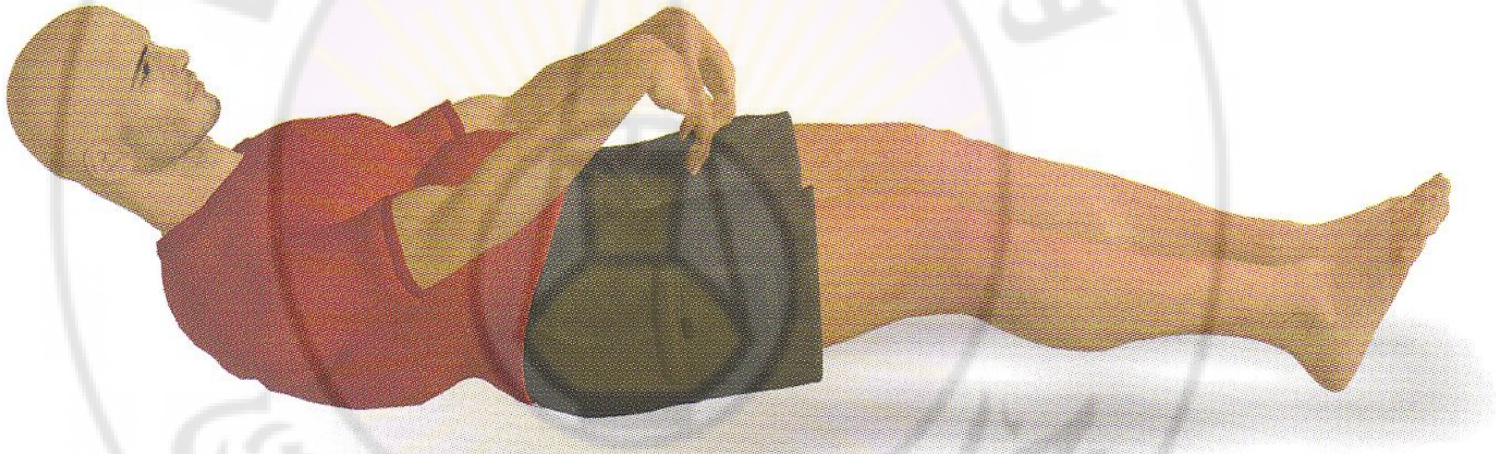
The eyes open immediately after the onset and remain open during the whole period of GTCS. They usually close post-ictally . Asymmetrical postures may occur both in PGTCS and SGTCS (Primary GTC-Secondary GTC)

The “Sign 4” Position

SGTCS

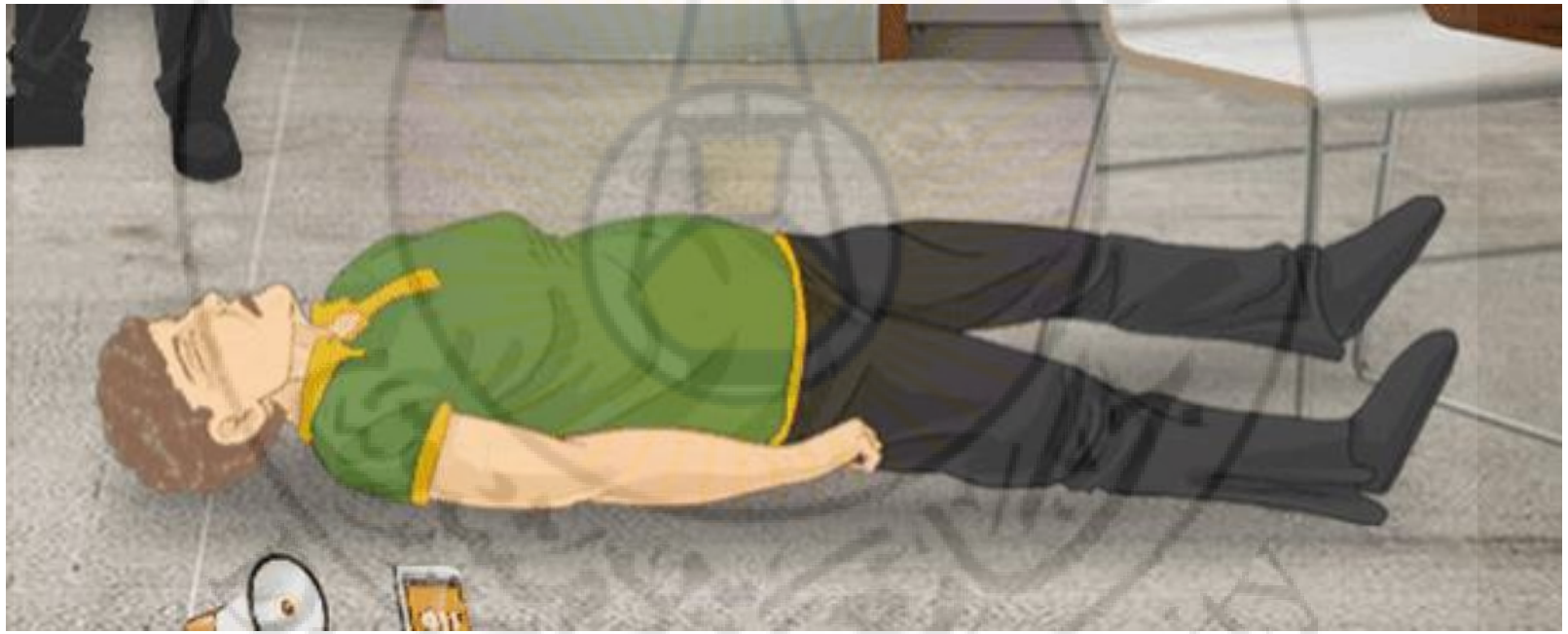
It is of lateralising significance when it occurs at the onset of a GTCS

Tonic Stage: Second Stage in Extension



Forced closure of the previously wide-open mouth which causes tongue biting
Epileptic cry
Cyanosis

Clonic Stage

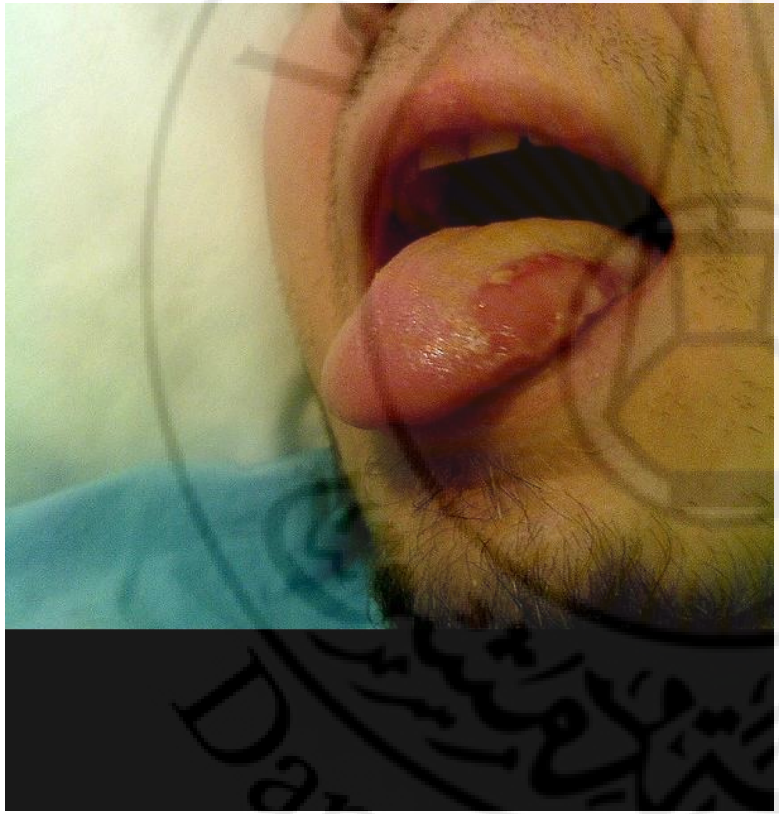


Post-ictal Stage

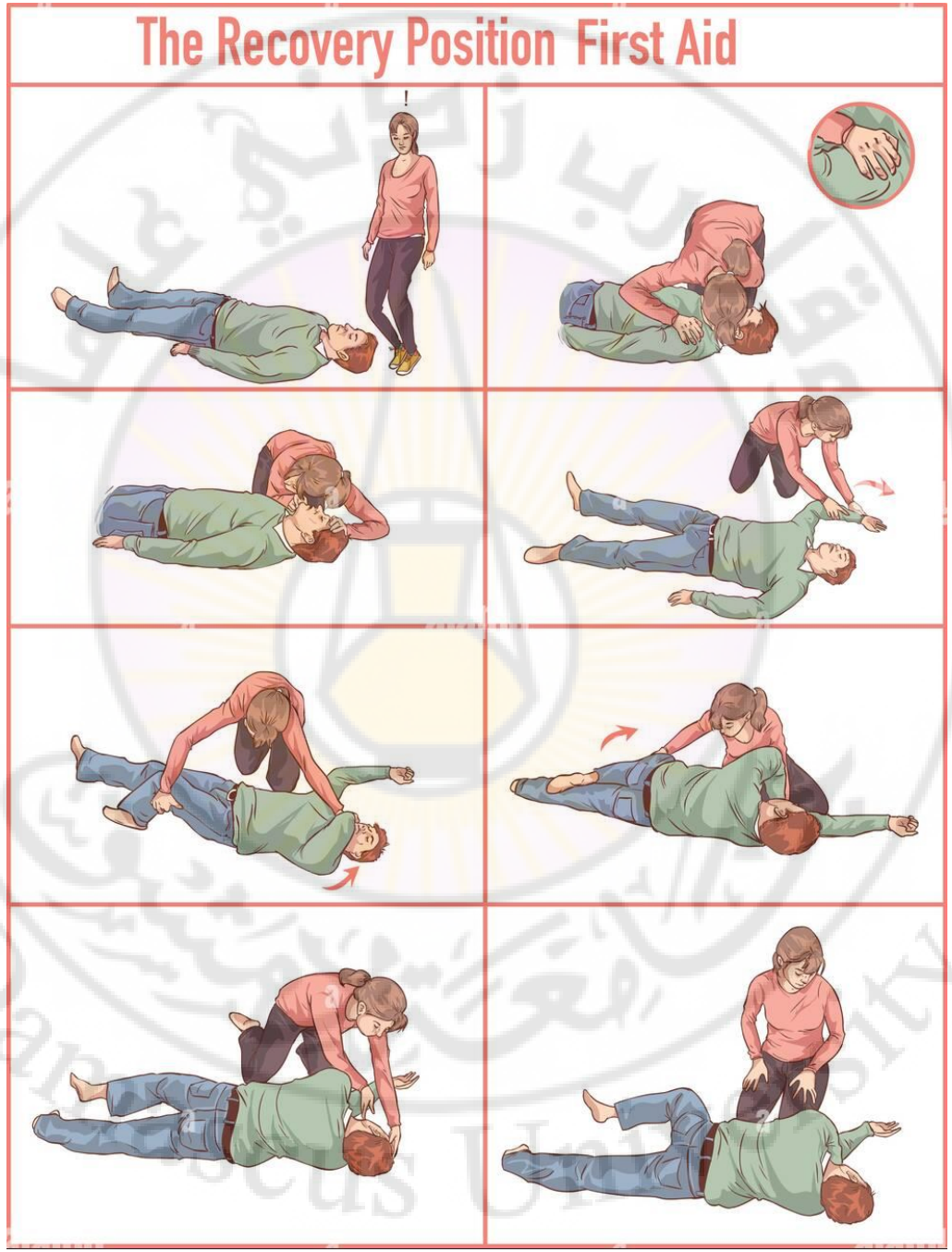
Immediate post-ictal stage with urinary incontinence

Urinary incontinence occurs in the immediate post-ictal stage and not during the convulsions

Lateral Tongue Bite



The Recovery Position First Aid



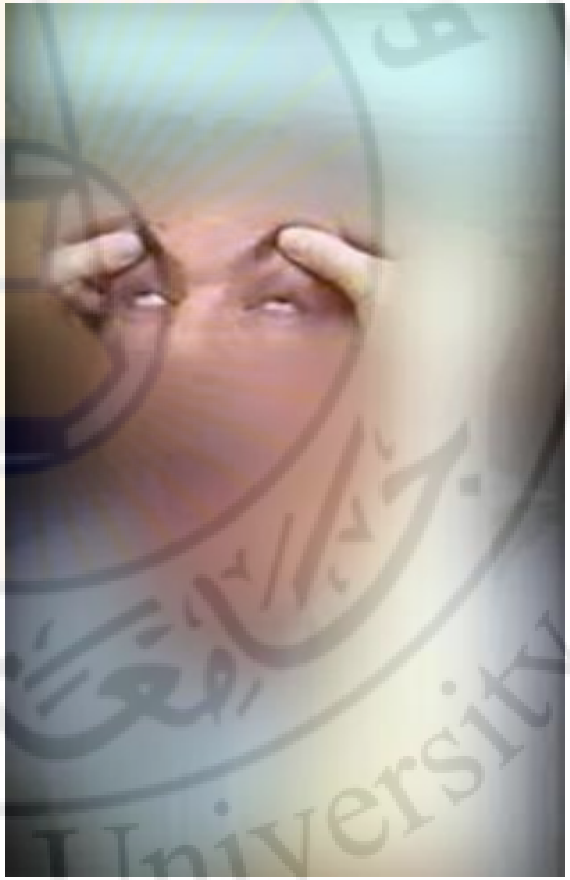
‘Psychogenic non-epileptic’ attacks

Psychogenic attack

Occurs in front of people
No injury
Prolonged attack
Red in face
Attempt to open the eyes may lead to voluntary contractions of the orbicularis oculi and upward deviation of the eyes.
Allowing the limp hand to fall on the face may be resisted.

Psychogenic attack

Attempt to open the eyes may lead to voluntary contractions of the orbicularis oculi and upward deviation of the eyes.



Hysterical Epilepsy

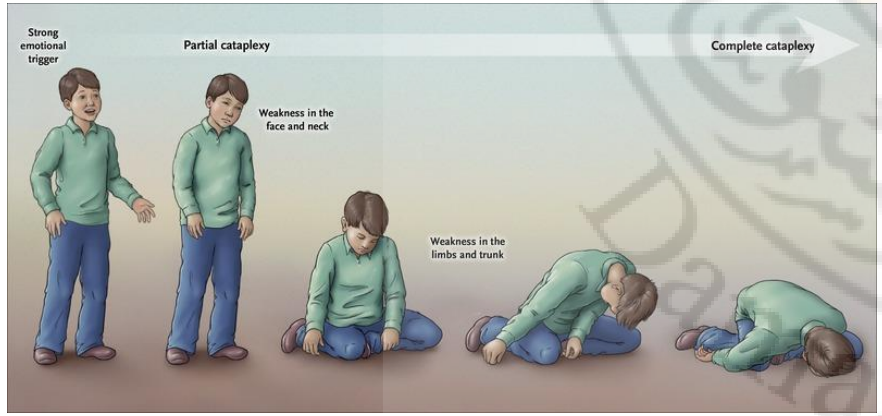
Hysterical Epilepsy

Fig. 2. Phase des contorsions
(Arc de cercle.)

A. Delahaye et E. Lecrosnier

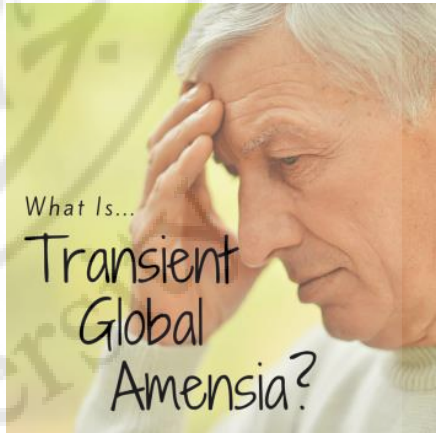
Narcolepsy

- Sudden irresistible need to sleep, for short periods
- Legs give way, when highly amused or angry



Transient global amnesia

A short period, lasting hours, of very selective memory loss, other cerebral functions remaining intact



Common Narcolepsy Symptoms

Excessive daytime sleepiness (EDS)

Bouts of muscle weakness (Cataplexy)

Hallucinations

Sleep paralysis

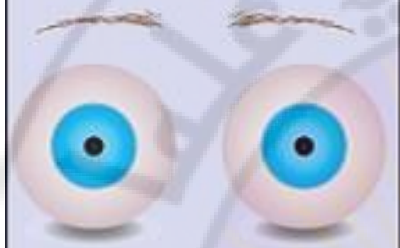
Diagnostic criteria for definite transient global amnesia

- Attacks must be witnessed and information available from a capable observer who was present for most of the attack
- There must be clear-cut anterograde amnesia during the attack
- Clouding of consciousness and loss of personal identity must be absent, and the cognitive impairment limited to amnesia (i.e. no aphasia, apraxia)
- There should be no accompanying focal neurological symptoms during the attack and no significant neurological signs afterwards
- Epileptic features must be absent
- Attacks must resolve within 24 hours
- Patients with recent head injury or active epilepsy (i.e. remaining on medication or one seizure in the past 2 years) are excluded

Unconsciousness

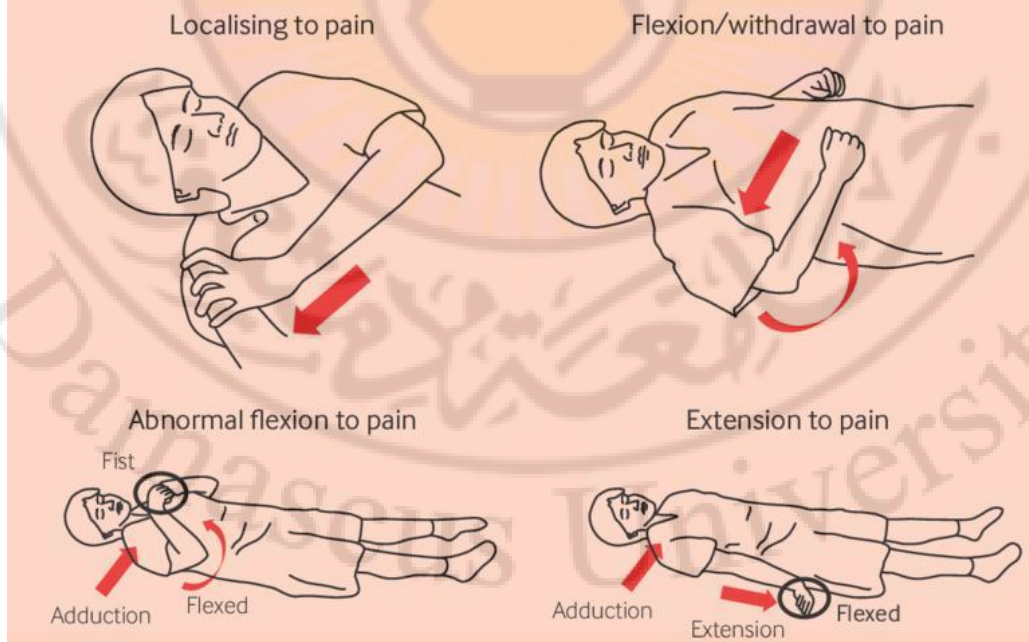
Persistent coma

GLASGOW COMA SCALE (GCS)

Behaviour	Response
 Eye Opening Response	4. Spontaneously 3. To speech 2. To pain 1. No response
 Verbal Response	5. Oriented to time, person and place 4. Confused 3. Inappropriate words 2. Incomprehensible sounds 1. No response
 Motor Response	6. Obeys command 5. Moves to localised pain 4. Flex to withdraw from pain 3. Abnormal flexion 2. Abnormal extension 1. No response

"Grip my finger" "Make a fist"	**M6** Obeys commands
Trapezius squeeze Supraorbital pressure	**M5** Localises pain
Flexion of limbs	**M4** Flexion/withdrawal to pain
Adduction and internal rotation of upper limbs Extension of lower limbs	**M3** Abnormal flexion to pain
Extension of upper and lower limbs	**M2** Extension to pain
No motor response	**M1** No response

Clinical tips



Unprompted eye opening → **E4** Spontaneous eye opening

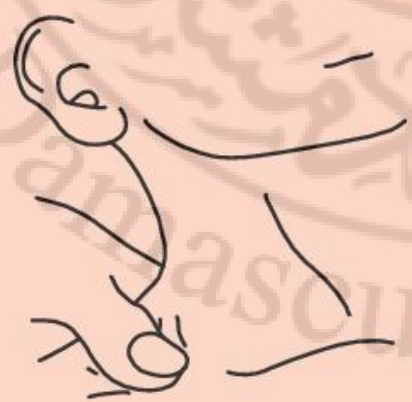
"Hello, open your eyes" → **E3** Eyes open to speech

Trapezius squeeze / Supraorbital pressure → **E2** Eyes open to pain

No eye opening → **E1** No response

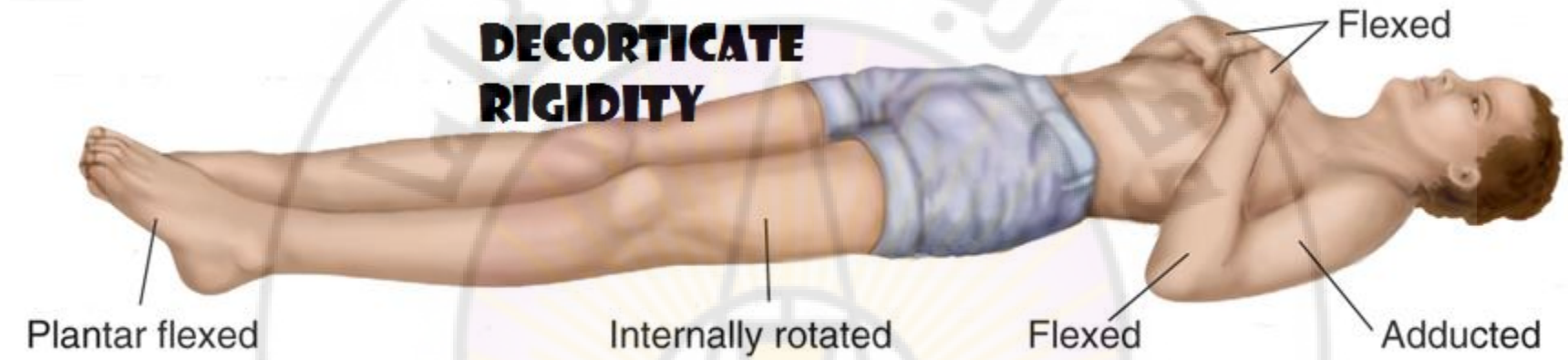
Clinical tips for painful stimulus

Trapezius squeeze

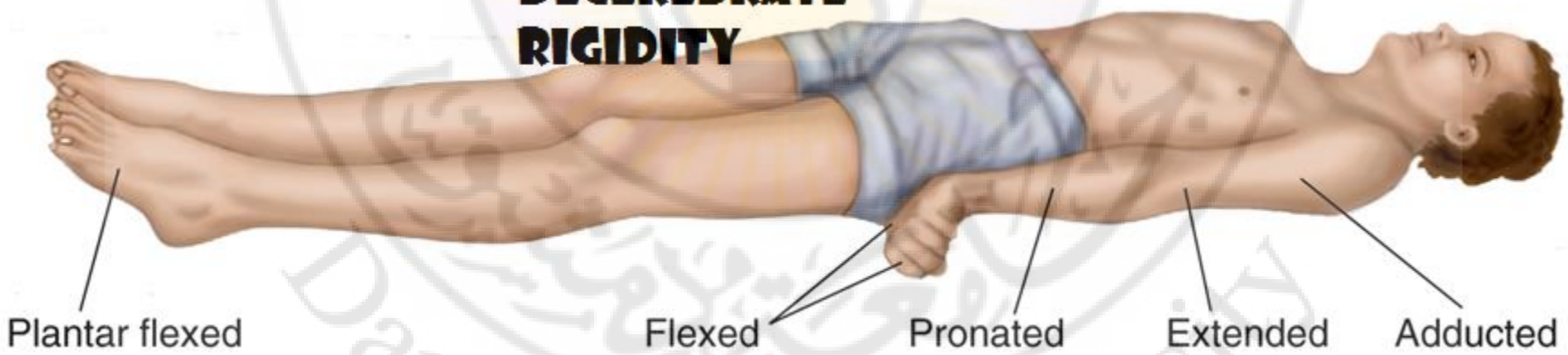


Supraorbital pressure

DECORTICATE RIGIDITY



DECEREBRATE RIGIDITY



GCS-P

* Important changes highlighted in red

	Motor response	Verbal response	Eye opening
1.	None	None	None
2.	Extension	Sounds	To Pressure
3.	Abnormal flexion	Words	To speech
4.	Withdrawal	Confused	Spontaneous
5.	Localizing	Orientated	
6.	Obeying commands		

Pupil Reactivity Score: Subtracted from the calculated GCS

Pupil Reactivity Score

Pupil(s) unreactive to light	Score
Both pupils	2
One Pupil	1
Neither pupil	0

For total GCS, subtract pupil reactivity score from calculated GCS

Content currated by Dr. Nicholas Schouela and infographic created by Dr. Shahbaz Syed, University of Ottawa, Department of Emergency Medicine

GCS-P = GCS – PRS

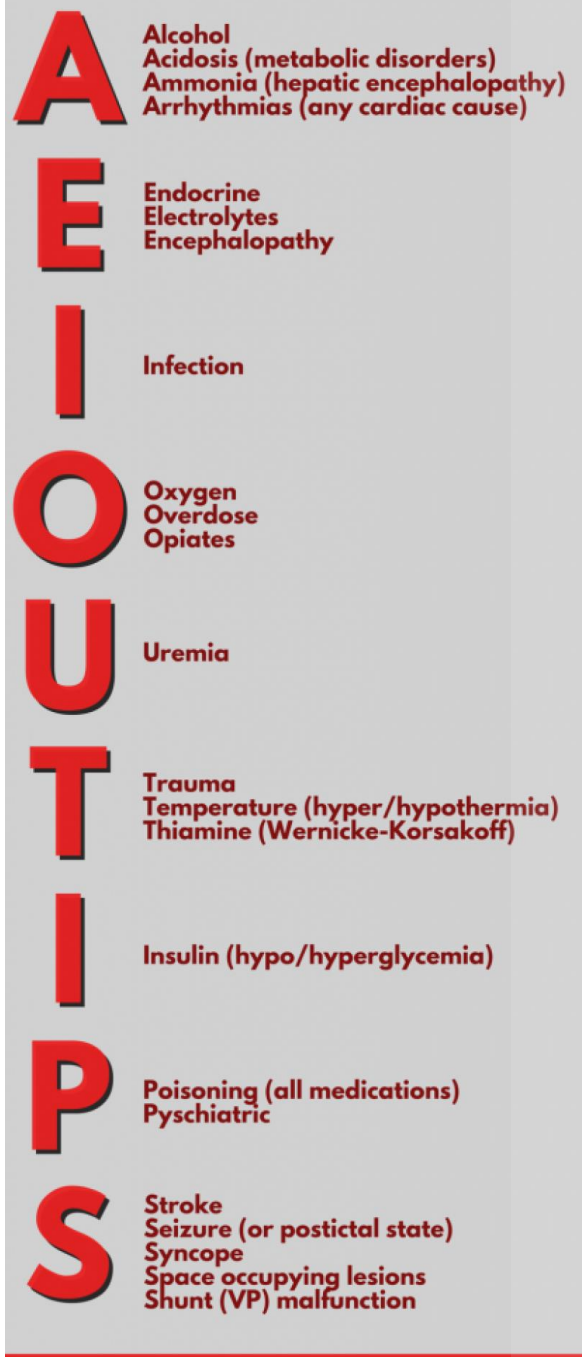
Pupil Reactivity Score

Pupils Unreactive to Light	Pupil Reactivity Score
Both Pupils	2
One Pupil	1
Neither Pupil	0

Note: the higher score is assigned to non-reactive pupils[5]

37 year old female with a traumatic subarachnoid hemorrhage (SAH). On presentation to the ED, she does not open her eyes, she moans, and displays abnormal flexion in her limbs to pain. On examination of her pupils they are both fixed and dilated.

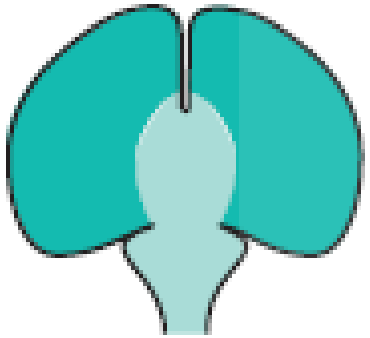
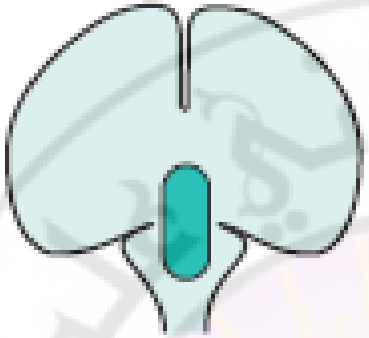
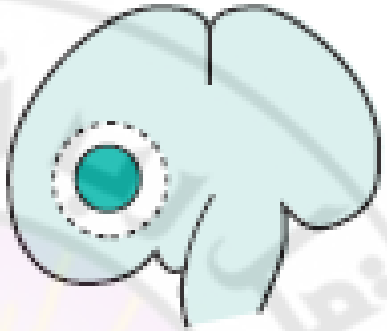
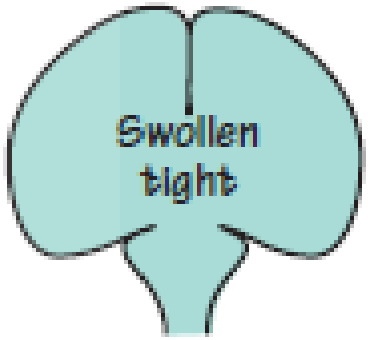
Her GCS is 6. Her GCS-P is 6-2 = 4.

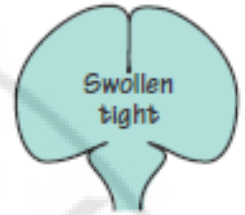


A E I O U	
A = Apoplexy	Brainstem infarction Intracranial haemorrhage
E = Epilepsy	Post-ictal or inter-ictal coma Status epilepticus
I = Injury	Concussion—major head injury
I = Infection	Meningo-encephalitis Cerebral abscess
O = Opiates	Standing for all CNS depressant drugs, including alcohol
U = Uraemia	Standing for all metabolic causes for coma. Quite a useful way of remembering all possibilities here is to think of coma resulting from extreme deviation of normal blood constituents

Oxygen	Anoxia
Carbon dioxide	Carbon dioxide narcosis
Hydrogen ions	Diabetic keto-acidosis
Glucose	Hypoglycaemia
Urea	Renal failure
Ammonia	Liver failure
Thyroxine	Hypothyroidism

A simple mnemonic for the recall of the causes of coma

			
Mechanism of coma Generalized impairment of cerebral hemisphere function, leading to a sub-standard response to normal afferent stimulation	Major primary pathology in the brainstem, depriving the cerebral hemispheres of their normal afferent stimulation	Unilateral cerebral hemisphere mass lesion, causing downward herniation of the medial part of the temporal lobe through the tentorial hiatus, which results in a sideways and downward shift of the brainstem. This situation of secondary brainstem malfunction is one form of 'coning', and explains such patients' coma. It may progress to medullary coning at foramen magnum level, if the mass lesion is left untreated.	Generalized impairment of cerebral hemisphere function, associated with bilateral cerebral hemisphere swelling. Bilateral medial temporal herniation occurs. Downward shift of the brainstem occurs at the level of the midbrain (tentorial hiatus) and medulla (foramen magnum). Coma is due to both generalized impairment of cerebral hemisphere function and coning at midbrain and medullary levels.

			
Cause of coma Overdose of CNS sedative drugs Severe alcoholic intoxication Diabetic comas Renal failure Hepatic failure	Brainstem infarction by basilar artery occlusion Brainstem haemorrhage, as occurs in severe hypertension	Haematoma Abscess Tumour	Brain trauma Meningo-encephalitis Cerebral anoxia or ischaemia Status epilepticus
Assessment of coma Glasgow Coma Scale works really well in these patients, since there is no focal neurological damage, and therefore no lateralizing or focal signs. In severe instances, the noxious process may involve the brainstem as well as the cerebral hemispheres. Signs of depressed brainstem function appear . . . impaired pupils and impaired regulation of vital functions	These patients have a multitude of abnormal neurological signs, since the major brainstem lesion is causing malfunction in the: • descending motor pathways • ascending sensory pathways • pathways to and from the cerebellum • cranial nerve nuclei • centres regulating vital functions	These patients have the signs of a unilateral cerebral hemisphere lesion and raised intracranial pressure (papilloedema). In addition the signs of coning (pupillary dilatation and impaired regulation of vital functions) may appear	These patients have the signs of bilateral cerebral hemisphere malfunction and raised intracranial pressure (papilloedema). They too may show signs of coning
	In these patients, the assessment of eyes, speech and motor responses, needed for the Glasgow Coma Scale, is somewhat interfered with, because of the presence of the primary neurological deficit produced by the primary CNS pathology. In such instances, the best eye, speech and limb response which can be achieved (in either of the two eyes, or in any of the four limbs) is the one which is used for the Coma Scale assessment. Despite this interference the Coma Scale, charted at intervals as shown in Fig. 11.3, provides a very valuable guide to an unconscious patient's progress		

- Airway
- Level of coma
- Cause of coma
- Caution over lumbar puncture
- Treat cause
- Routine care of unconscious patient

COMA COCKTAIL

Thiamine 100mg IV,
50% DW 50ml,
Naloxone 0.4-0.8 mg IV,
Flumazenil 0.2-1.0 mg IV

هل هناك شخص يمكن أن يعطي معلومات مفيدة

Clues obtained from the patient's

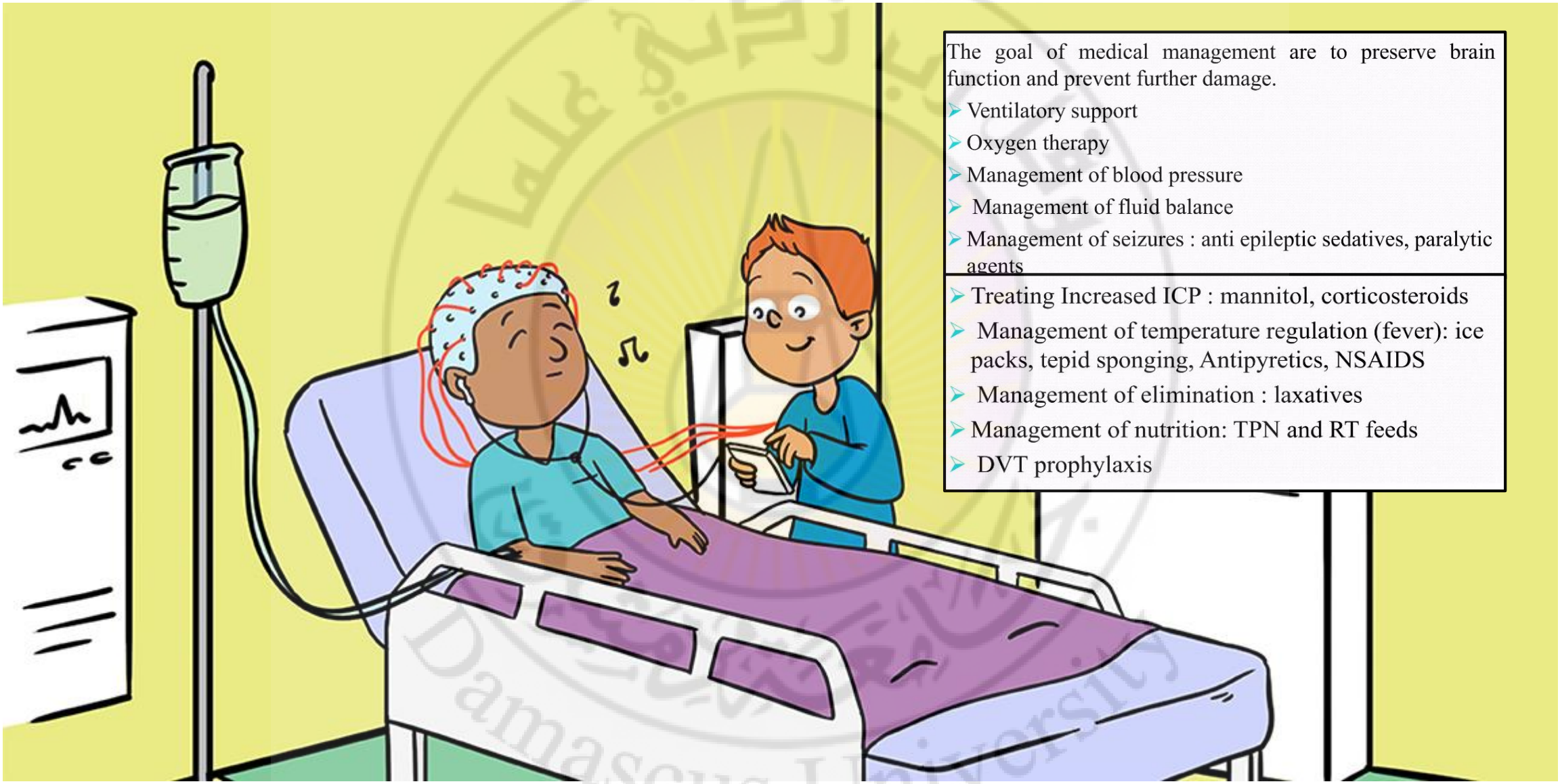
- Clothing or
- Handbag

Relatives

Paramedics

Ambulance personnel

Bystanders particularly about the mode of onset



The goal of medical management are to preserve brain function and prevent further damage.

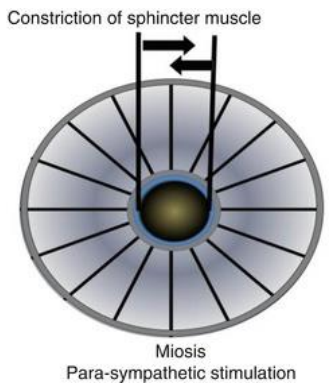
- Ventilatory support
- Oxygen therapy
- Management of blood pressure
- Management of fluid balance
- Management of seizures : anti epileptic sedatives, paralytic agents
- Treating Increased ICP : mannitol, corticosteroids
- Management of temperature regulation (fever): ice packs, tepid sponging, Antipyretics, NSAIDS
- Management of elimination : laxatives
- Management of nutrition: TPN and RT feeds
- DVT prophylaxis

Brainstem Reflexes

The brainstem reflexes that are examined are

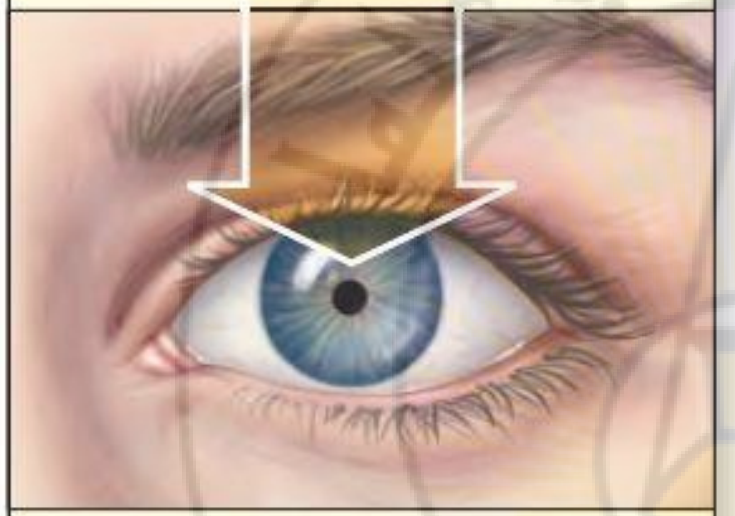
1. Pupillary reflex
2. Ocular movements
3. Corneal reflex
4. Respiratory pattern

- As a rule, coma due to bilateral hemispheral disease preserves these brainstem activities

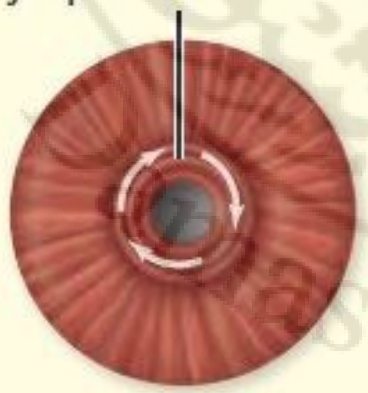


Pupillary constriction

Bright light



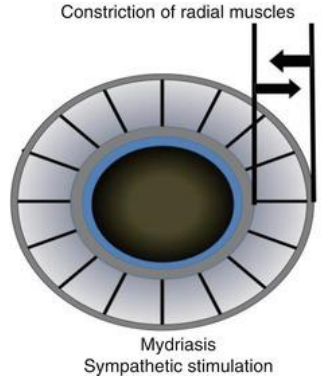
Sphincter pupillae
contracts
(parasympathetic innervation)



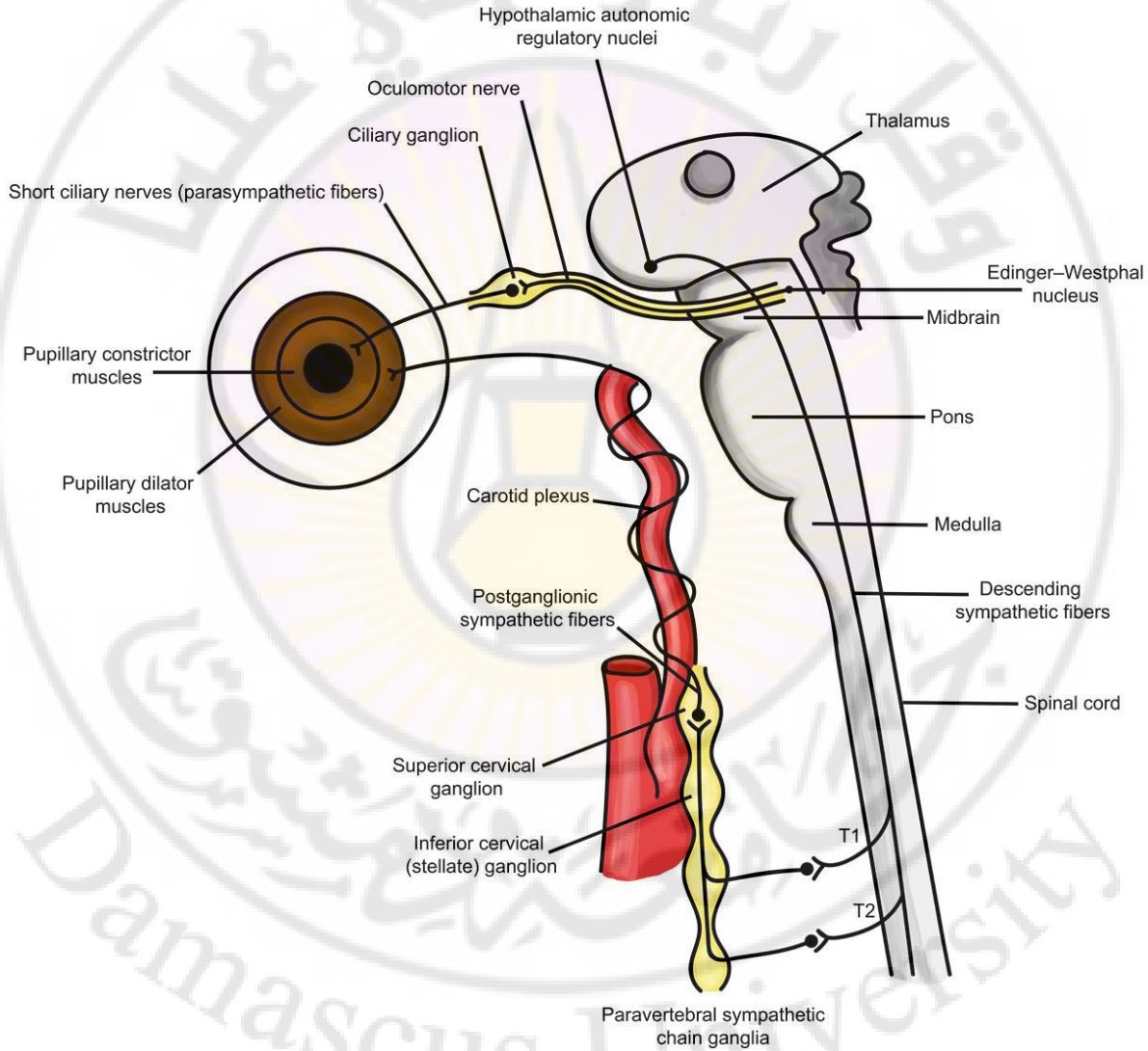
Pupillary dilation

Low light

Dilator pupillae
contracts
(sympathetic innervation)

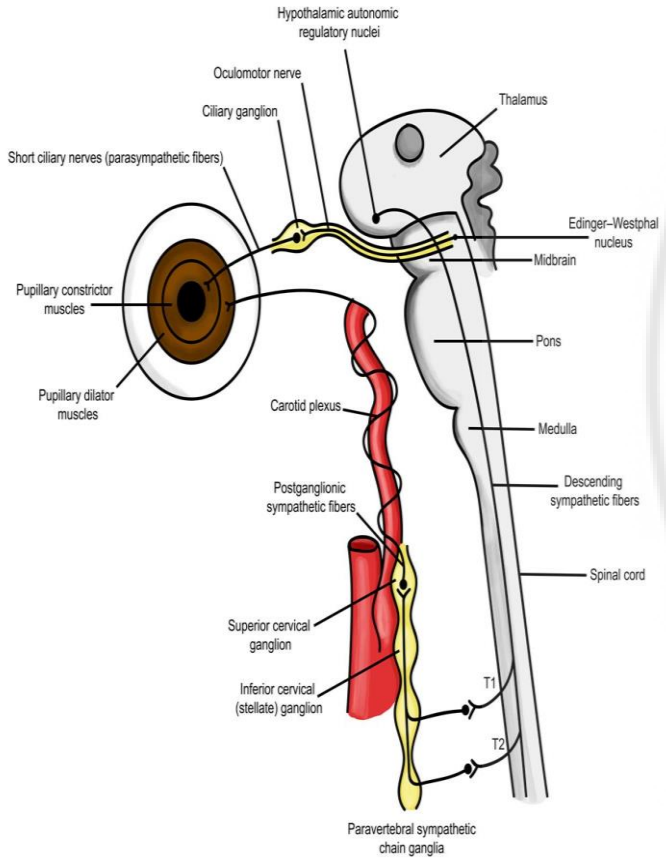


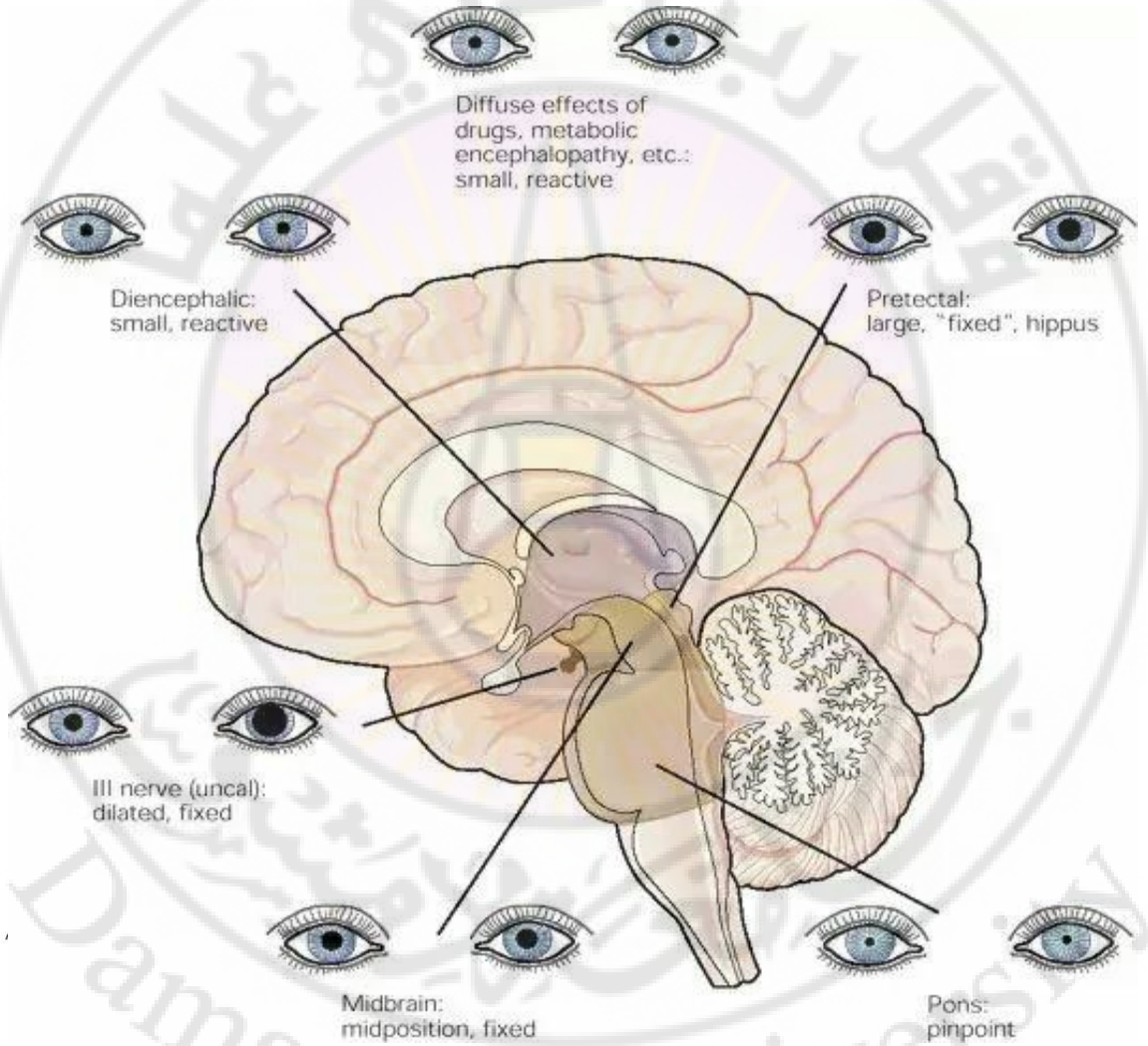
Autonomic Innervation of the Eye



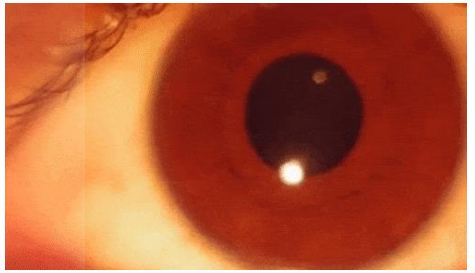
Moises Dominguez

حجم الحدقة





Pupillary hippus, also known as pupillary athetosis, is **spasmodic, rhythmic, but regular dilating and contracting pupillary movements between the sphincter and dilator muscles**



الحدقة والسبات:

بإصابة القشر المخي : لا تتأثر الحدقة.

بإصابة الدماغ البيني : تضيق الحدقة مع ارتكاس للنور بسبب اصابة الودي.

اصابة الدماغ المتوسط : حدقة متوسطة الحجم مع غياب الارتكاس ،لإصابة الجملتين الودية و اللاودية.

إصابة الجسر : حدقة دبوسية لإصابة الودي.

إصابة البصلة : قد تتضيق الحدقة مع بقاء الارتكاس لكنها غالبا لا تتأثر .

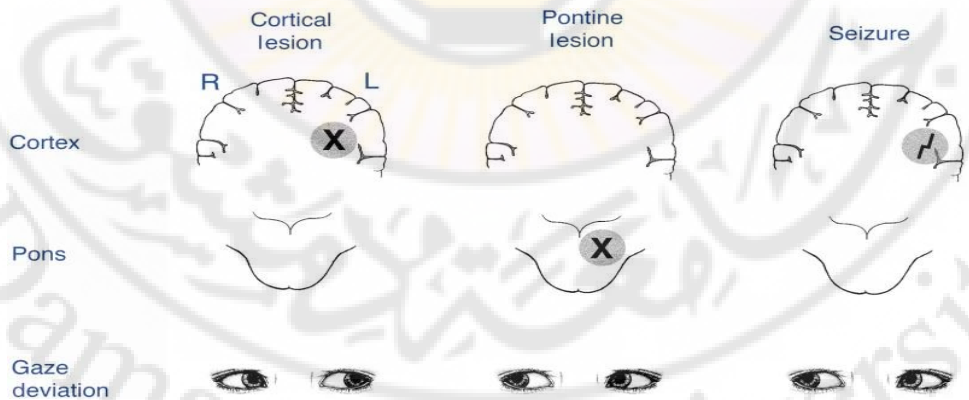
سبات استقلابي : لا تتأثر الحدقة –هام جدا.

تسمم بالاتروبين :حدقة متوسعة لارتكاس الضياء .

تسمم بالمورفين او مركبات الفوسفور العضوية : حدقة دبوسية .

Ocular movements

- The position of the eyes at *rest*
- Presence of *spontaneous eye movement*
- The reflex responses to oculocephalic and oculovestibular maneuvers



The eyes look toward a hemispheral lesion and away from a brainstem lesion.

Common abnormal eye positions in unconscious patients

a Normal eye position. Pupillary size and papillary light response must be assessed.

b Horizontal conjugate deviation indicates hemispheric lesions. The gaze is directed toward the lesion. Lesions in the pons below the oculomotor nuclei and thalamus damage may produce tonic deviation away from the lesion. Differential diagnosis includes seizures.

c Upward deviation indicates bilateral hemispheric damage, such as that seen after extensive hypoxic-ischemic insult, after cardiac resuscitation or asphyxia.

d Downward eye deviation indicates lesions to the thalamus or to the dorsal midbrain, often caused by a massive thalamic hemorrhage extending in the mesencephalon.

e Skew deviation in the resting position is indicative of primary brainstem lesion, possibly in the region of the interstitial nucleus of Cajal. The higher eye often corresponds to site of damaged midbrain or pons.

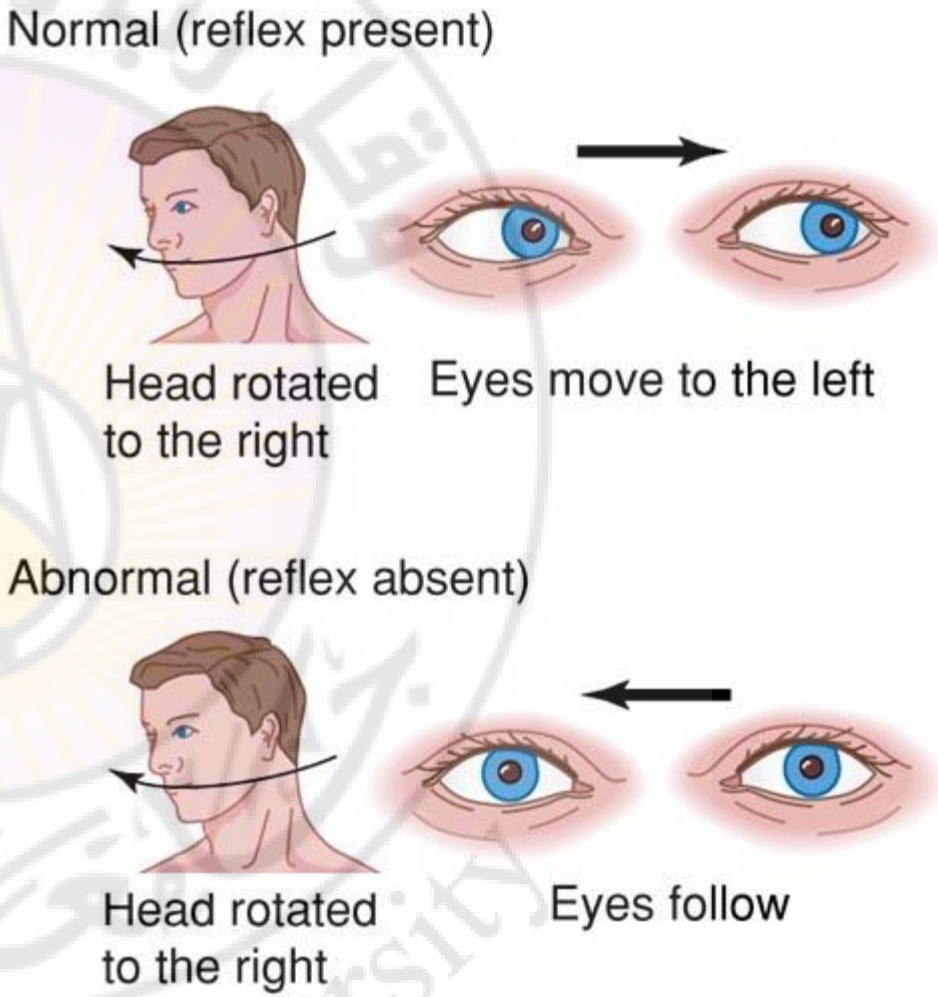
f Caloric stimulation with ice water, while the head is 30 • upright, stimulates horizontal canals and produces a tonic deviation toward the ear, but it may also reveal adduction paralysis (internuclear ophtalmoplegia).

The oculocephalic reflex

- The oculocephalic reflexes, elicited by moving the head from side to side or vertically and observing eye movements in the direction opposite to the head movement
- If the eyes move *conjugately* in the *opposite direction* to that of head movement, the response is positive and indicates an *intact pons* mediating a normal vestibulo-ocular reflex
- The "doll's eyes" refers to the reflex elevation of the eyelids with flexion of the neck

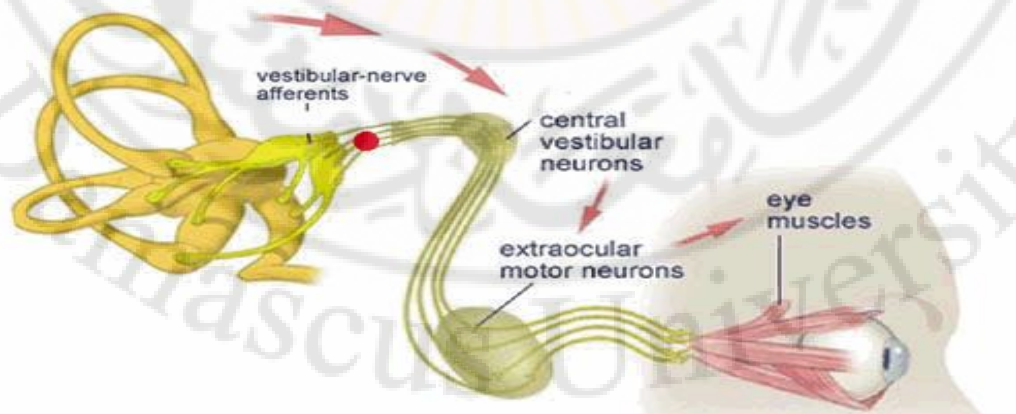
- These reflexes are normally suppressed in the awake patient


Normal Vestibulo-Ocular Reflex

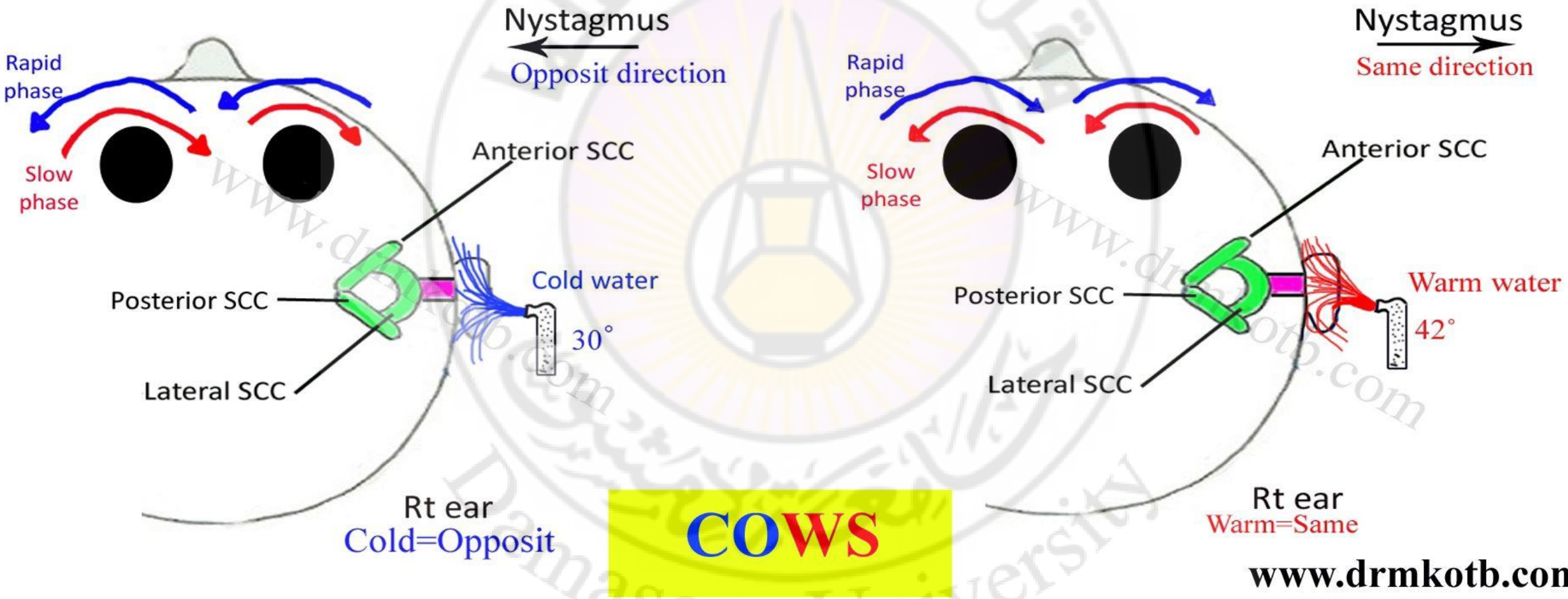

Normal (reflex present)
Head rotated to the right
Eyes move to the left
Abnormal (reflex absent)
Head rotated to the right
Eyes follow

The oculovestibular reflex

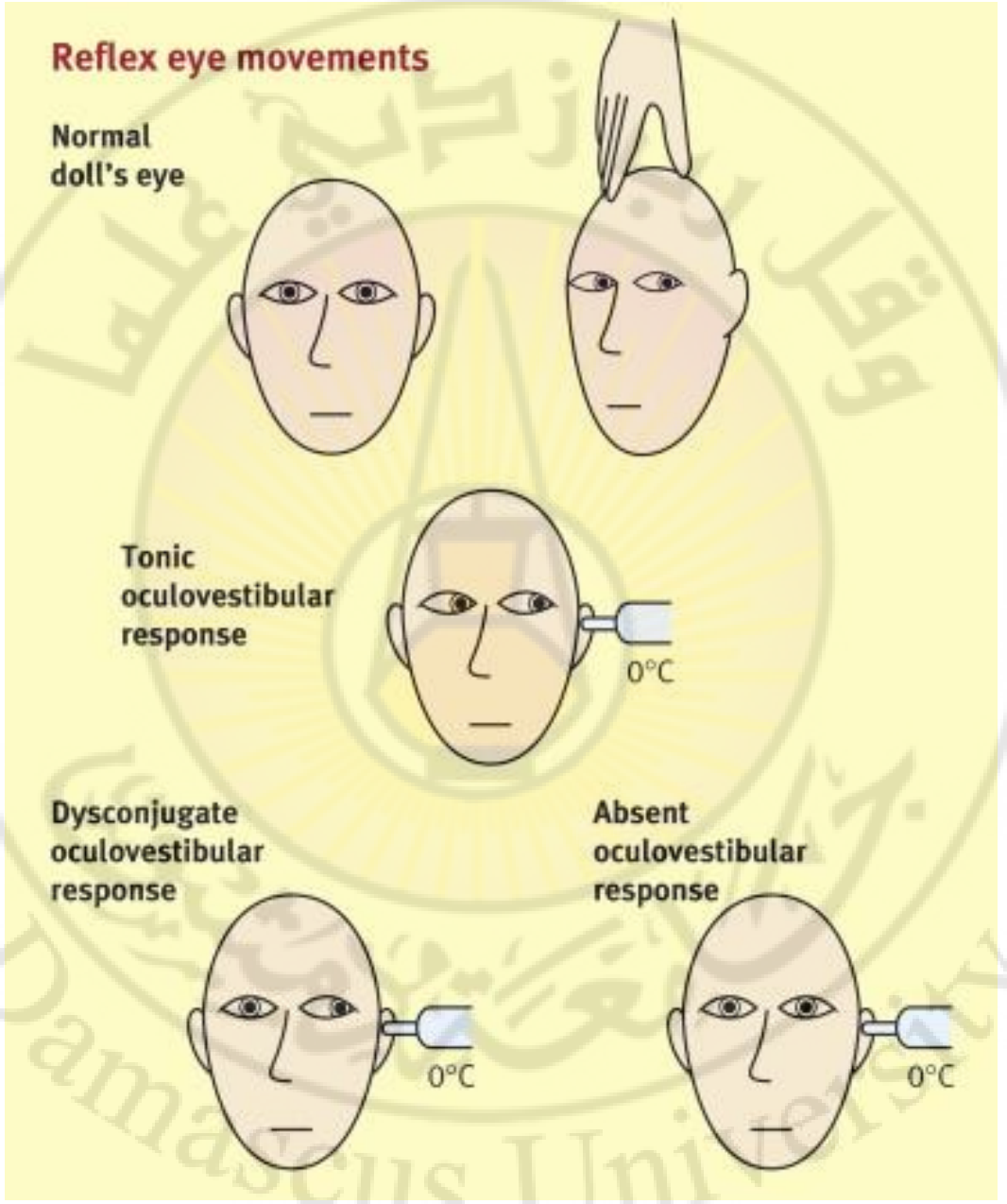
- These are tested by the installation of ice-cold water into the external auditory meatus, having confirmed that there is no tympanic rupture.
- A normal response in a conscious patient is the development of *nystagmus* with the *quick phase away* from the stimulated side This requires intact cerebropontine connections



Caloric test

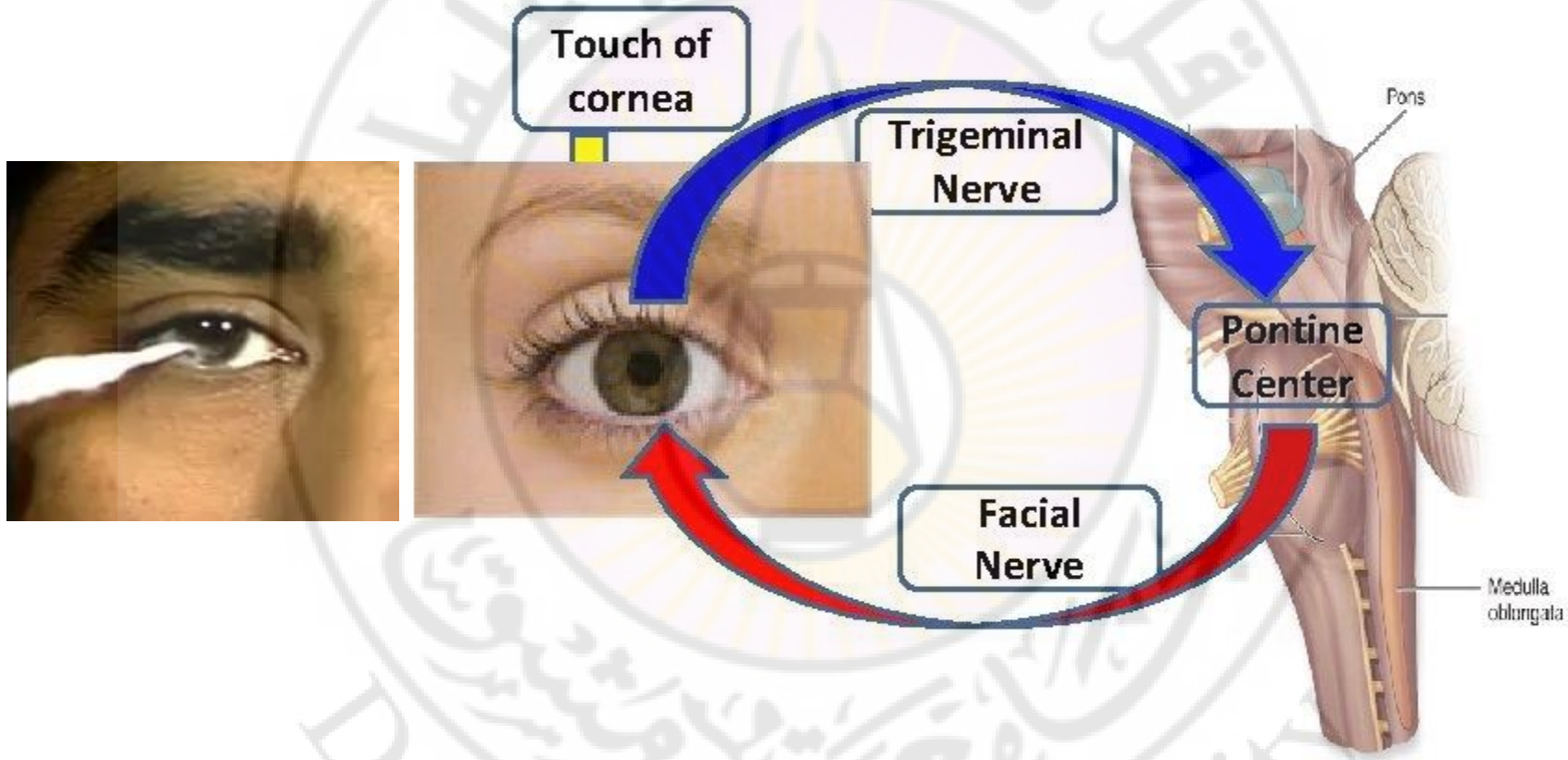


Cold-Opposite-Warm-Same



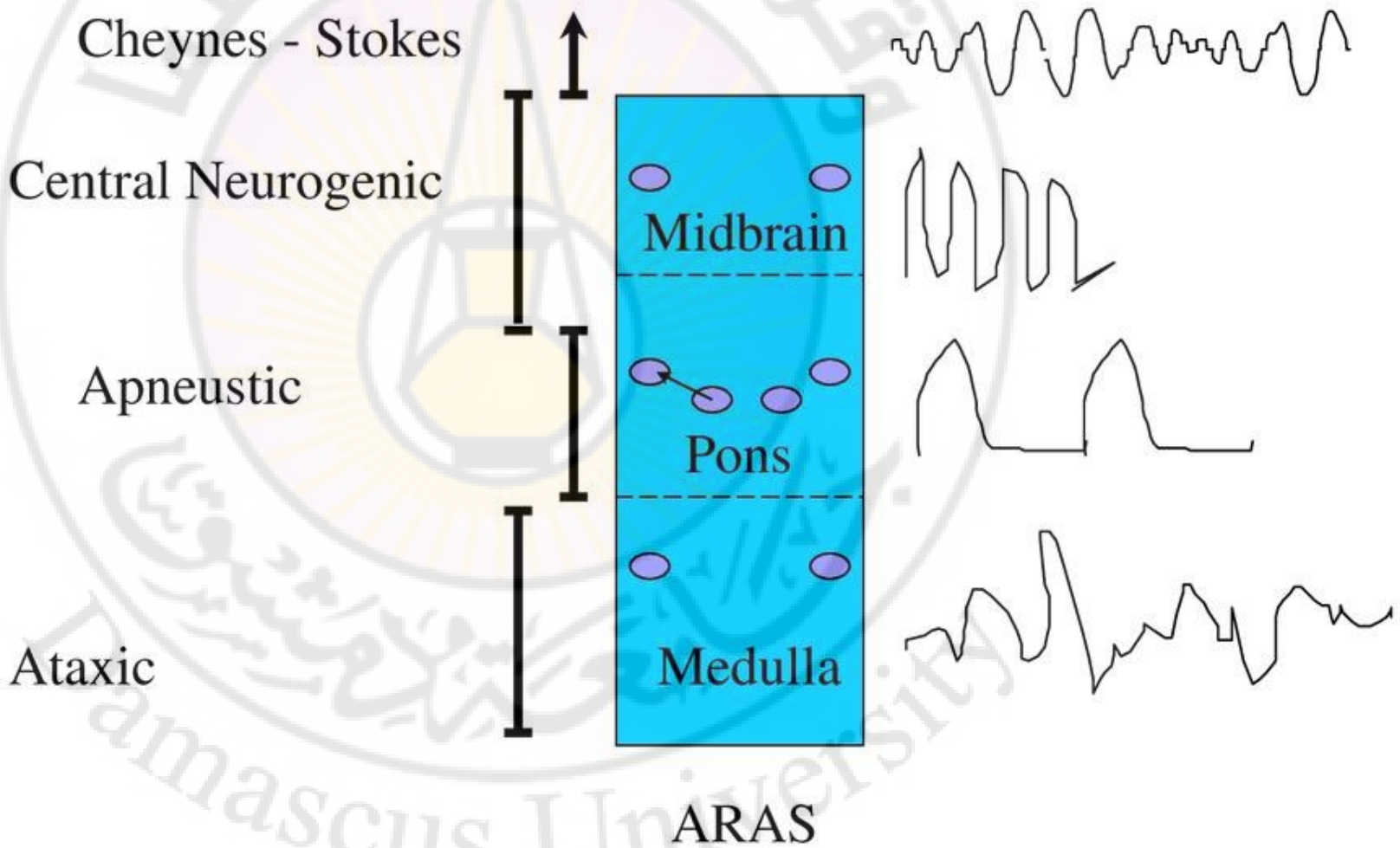
An asymmetric or absence of tonic deviation of eyes to the side of cold water irrigation confirms a problem in the brainstem

Corneal reflex



Cheyne-Stokes ⟶ Cerebrum
rapid-Shallow ⟶ mid brain
slow-gasping ⟶ Pons
Irregular ⟶ Medulla
GX

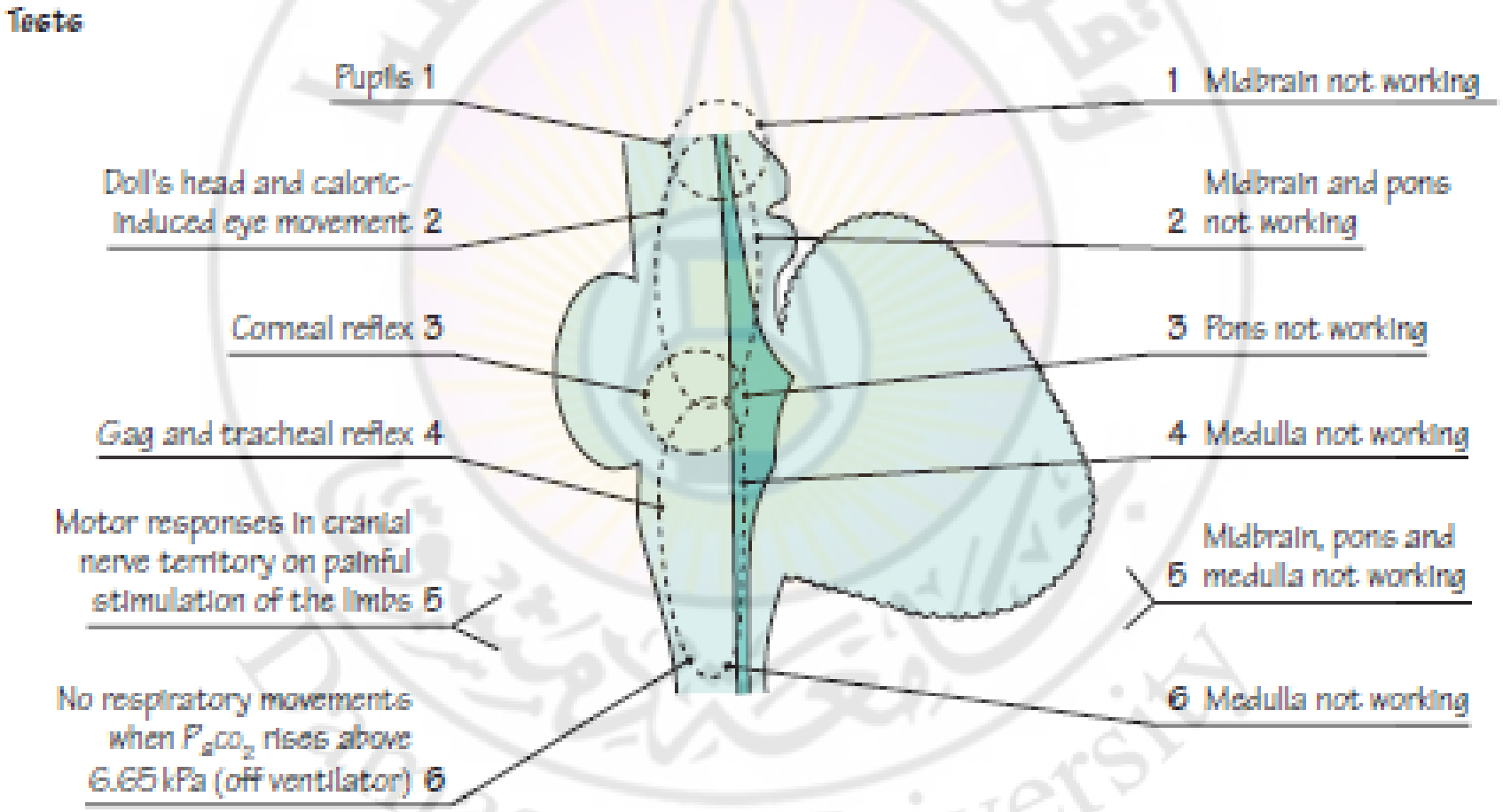
Abnormal breathing patterns in coma



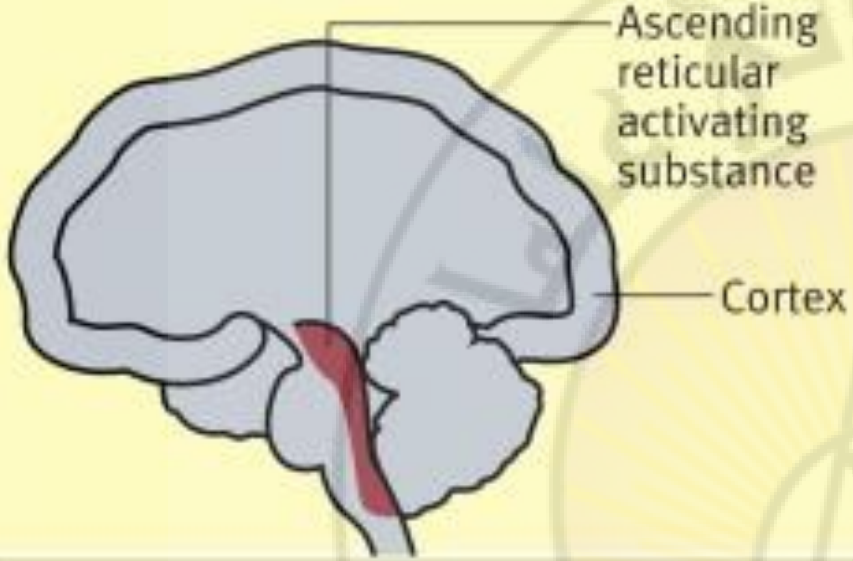
Brainstem death

Preconditions	
In coma on ventilator	The patient is deeply comatose, and maintained on a ventilator on account of failure of spontaneous respiration
Diagnosis certain	The coma is due to irreversible structural brain damage. The diagnosis is certain, and is a disorder which can lead to brainstem death
No drugs No hypothermia No metabolic abnormality	Any of which might be having a reversible effect on the brainstem
No paralytic drugs	The patient's unresponsiveness is not due to neuromuscular paralytic agents

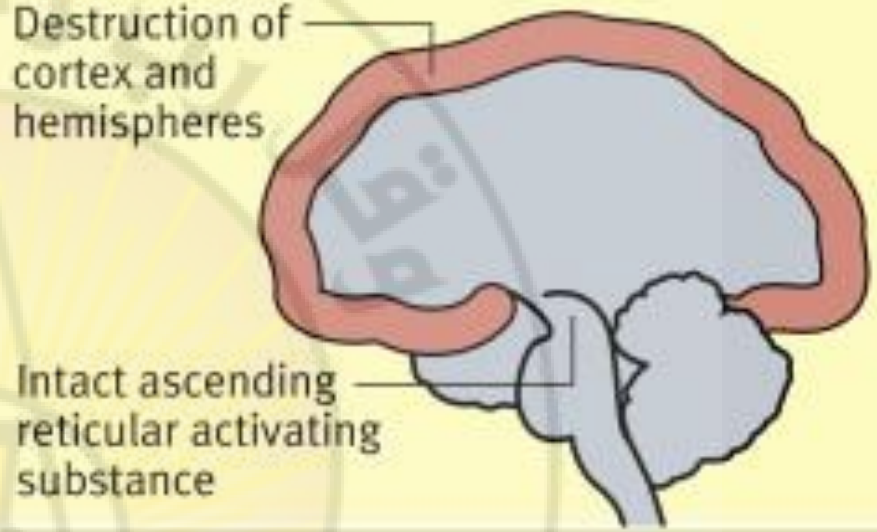
Brainstem death



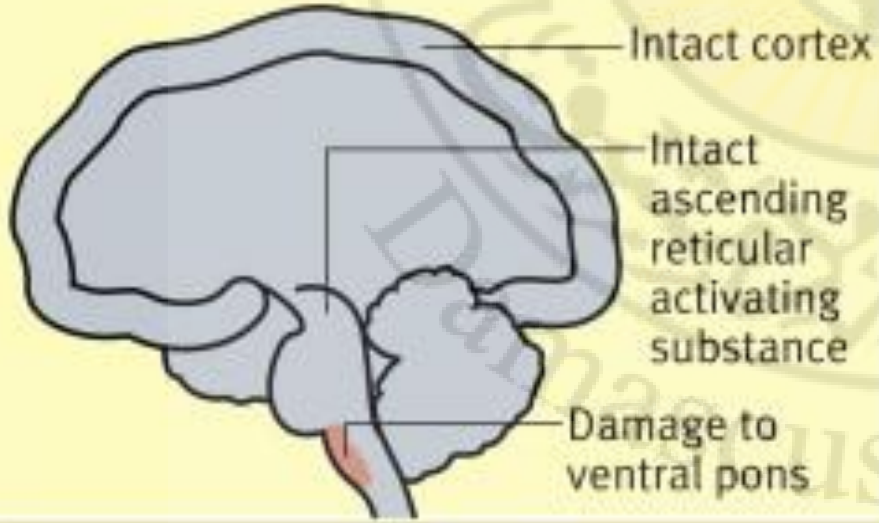
Normal consciousness



Vegetative state



Locked-in syndrome



Brain stem death


THANK YOU!