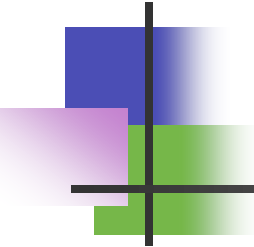


Lecture III

Malformations and developmental disorders



Overview

- Unknown etiopathogenesis
- Genetic association
- Toxic compounds
- Infectious agents

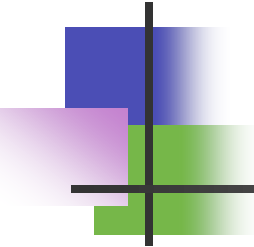
→ Failure of closure of neural tube

Neural tube defect

- Midline → location
- Involve
 - Neural tissue
 - Meninges
 - Bone and soft tissue → Primary defect
- The most common CNS malformation

يمكن ان يحصل العكس انما اذا bone يصير فيه defect
نحوه ان يكون في العكس على neural tube

→ Fail to close as a result of neural tube defect 'secondary'



Neural tube defect

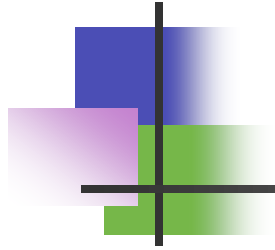
- Pathogenesis
 - Failure of neural tube closure, with secondary mesenchymal tissue defect
 - Anencephaly ✓
 - Myelomeningocele ✓
 - Primary bony defects
 - Encephalocele ✓
 - Meningocele ✓
 - Spina bifida ✓

Neural tube defect

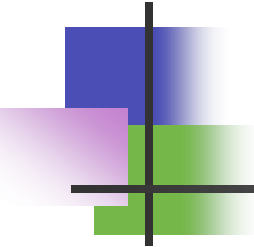
■ Morphology

- Anencephaly → Defective development of brain tissue
- Myelomeningocele → Defect that involve both the SC and brain
 - Lumbosacral region *most commonly*
 - Motor and sensory deficit of lower limbs
 - Incontinence
 - Infection *The cause of mortality*
- Encephalocele → Outpouching of meninges/membranes
 - Occipital
 - Nasal area
- Spina bifida → Split spine
 - The most common NTD
 - May be occult → with no symptoms



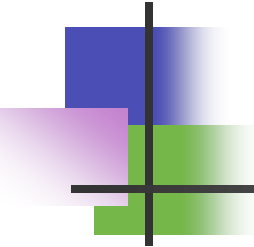


Cerebral edema



Cerebral edema

- Increased intracranial pressure
 - Cerebral edema → *Most common*
 - Increased CSF volume
 - Expanding mass



Cerebral edema

- Pathways

- Vasogenic edema *→ The problem concerning the BVs*
 - Increased EC fluid
 - Disruption of the BBB *→ The cause of vasogenic edema*
 - Paucity of lymphatics *→ Tolerance for edema formation is limited*
 - Localized
 - Around inflammation or neoplasm
 - Generalized
 - Global ischemic injury

Cerebral edema

- Pathways

- Cytotoxic edema

- Increased IC fluid secondary cell injury
 - Due to generalized hypoxia/ischemia
 - Or metabolic derangement

→ deficiency of ATP

↳ ↑ plasma membrane permeability
↳ Pumps function will cease

- Both are involved in generalized edema

Hydrocephalus

- Definition → ↑CSF

- Circulation

- 1 ■ Produced by choroid plexus

- 2 ■ Through ventricles

- Through foramina Luschka and Magendie →

زائکنا اتصال بینہ ار
Subarachnoid, ventricles

- 3 ■ Subarachnoid space

- 4 ■ Absorbed by the arachnoid granulations

Hydrocephalus

Obstruction of foramina luschka or Magendie

- Most cases are related to impaired flow and resorption
- Overproduction by tumors of choroid plexus is rare
- Dilation of ventricles
- Increased ICP

Results ←

→ More common in adults (after closure of sutures)
(نفس الصفة ثابتة للحد)

Hydrocephalus

- In infancy

- Enlarged head

- 2 types

- Obstructive (non communicating) → of foramina that communicate with the subarachnoid space
- Communicating → No obstruction
→ arachnoid absorption of the CSF

→ Luschka
Magendie

الكسلة في الحنك

→ very serious and high mortality rate

Raised ICP and herniation

- Displacement of brain tissue through the falx, tentorium and openings in the skull

→ Subfalcine herniation

← Trans tentorium herniation

→ foramen magnum
↳ Tonsillar herniation

- Mostly caused by mass effect
- Increased ICP may compress the vasculature exacerbating edema → vicious cycle

Raised ICP and herniation

- Morphology

- Subfalcine (cingulate)

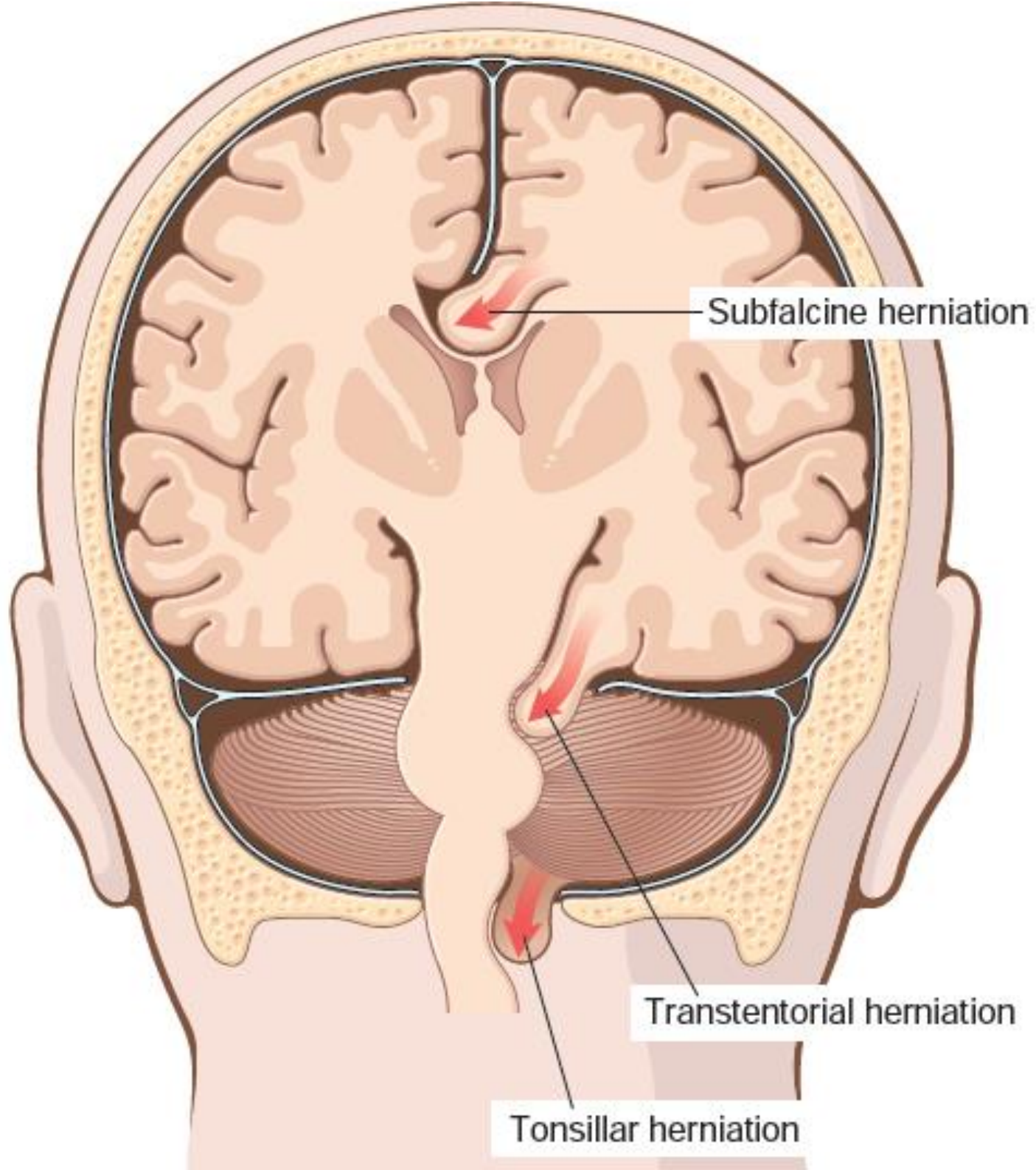
- Unilateral expansion → 1 hemisphere
- May lead to compression of the anterior cerebral artery

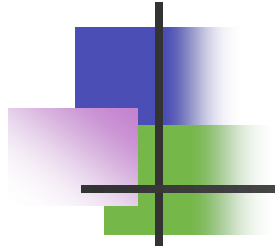
- Transtentorial (uncal)

- Medial aspect of the temporal lobe
- Compression of the III. Cranial nerve → Unilateral dilation of pupil
- Compression of the posterior cerebral artery
- Cerebral peduncle may be compressed
- Duret hemorrhages

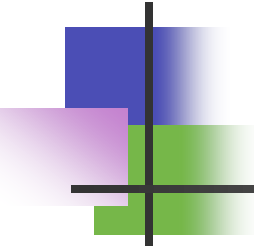
- Tonsillar

- Brain stem compression → Affects the vital centers of respiratory & CVS





Neurodegenerative diseases



Neurodegenerative diseases

- Progressive loss of particular groups of neurons with shared functions
- Accumulation of protein aggregates “proteinopathy”
 - Due to mutations *↳ Have main role in pathogenesis of these diseases*
 - Alter conformation, or processing or clearance
 - Imbalance between synthesis and clearance
 - Related to genetic, environmental or stochastic factors

Neurodegenerative diseases

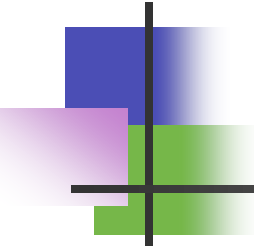
- Typically resistant to degradation
- Show aberrant localization in the neuron
- Sequestration of proteins into large aggregates that are not toxic
- Smaller aggregates are toxic

بعض امكانات معن در صدد بتواند
نيه رعايقها را امكانات بيگوني
سعي من المفترض انه يتواند فيه

لے سے متعلق منتقل بن مکان
للتاني رباتالي هضول تأثيرها
سعي نيا امكان الي هي موجودة
فيه

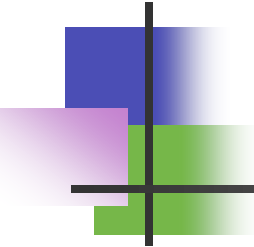
Neurodegenerative diseases

- Additional accumulation
 - Loss of protein function
 - Contribute to cell injury
 - May behave like a prion → *زمان کان موجود برهن*
Mad cow disease (جنون البقر)
 - May be taken up by another cell and provoke additional aggregation
 - The disease spread from one site to another
 - Not transmissible between individuals
- Recognized as inclusions
 - Diagnostic → *Maybe pathognomic*



Alzheimer disease

- The most common cause of dementia in older adults → 86 years
- Impairment of higher cognitive functions
- Deficits in (over a course of 5-10 years)
 - Memory
 - Visuospatial orientation → بقدرشن یحکمی دینعو موجود
 - Personality
 - Language
- Becomes profoundly disabled, mute and immobile
- 40% for 85-89 YO
- 5-10% are familial



Alzheimer disease; pathogenesis

- Accumulation of 2 proteins
 - A β $\rightsquigarrow$ Amyloid
 - Critical initiating event
 - Tau $\rightsquigarrow$ Microtubule binding protein
 - Insufficient to induce A β deposition
- In specific brain regions
- As a result of excessive production
- And defective removal

Alzheimer disease; pathogenesis

- 2 hallmarks

- Amyloid plaques

- Deposits of aggregated $A\beta$ peptides in the neuropil

- Neurofibrillary tangles

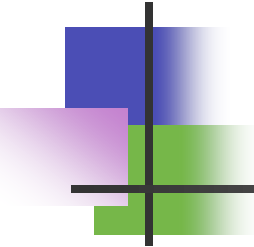
- Aggregates of the microtubule binding protein tau
- Persists after neuron death

- Both contribute to neuron dysfunction

لو رعت هيل ال 2 دتطبت
على brain هتكون ال neuropil
Brain tissue → neurons
neuroglia

العزّة انه $A\beta$ هو ال Pathognomic والمحرك للمرض
Tam ← specific ممكن يكون موجود بـ other neurodegenerative diseases

Alzheimer disease; morphology



- Cortical atrophy
 - Medial temporal lobe (hippocampus, entorhinal cortex, and amigdala) is involved early in the course
- Compensatory ventricular enlargement
 - ↳ due to brain atrophy

Sulci of the brain become
very deep and wide due to
gyri atrophy



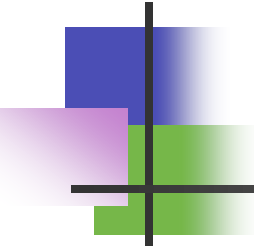
Alzheimer disease; morphology

- Neuritic (senile) plaques → *Amyloid plaques*
 - ✓ ■ Focal spherical collections of dilated, tortuous, axonal or dendritic processes (dystrophic neurites) often around a central amyloid core
 - Amyloid core mainly of A β
 - Forms as a result of cleavage of APP → *Amyloid precursor protein*
 - May be surrounded by a clear halo
 - Contain tau aggregates
 - Microglia and astrocytes at the periphery
 - Primary motor and sensory cortices are relatively spared
 - All deposition of A β in brain parenchyma is considered a form of AD → *A β accumulation = Alzheimer dz.*

Accumulation →

Alzheimer disease; morphology

- Neurofibrillary tangles → Tau
 - Tau containing bundles
 - Displace and encircle the nucleus → Neuron degeneration
 - Flame shape in the pyramidal neurons
 - In rounder cells globose tangles
 - Basophilic fibrillary structures
 - More clear by silver staining or IHC
 - Insoluble → حصة سائلة
 - Resistant to clearance in vivo
 - Remain visible after neuron death "gohst" or "tombstone" tangles سنج
 - In contrast to neuritic plaques, tangles are found in other neurodegenerative diseases → Thus not specific for AD



Parkinson disease (PD)

- Neurodegenerative disease
- Hypokinetic movement disorder
- Caused by loss of dopaminergic neurons from the substantia nigra
 - And thus reduction of dopamine content in the “striatum”

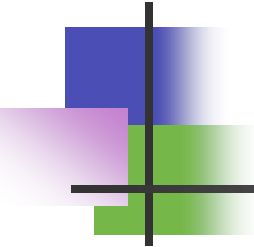
Parkinson disease (PD)

■ Clinical

- Masked facies → يتعثرش إذا مبتسم ولا يكثر
- Stooped posture → Bending forward الجسم منحني للذعام
- Festinating gait → بهمشي مشي سريع بس الخطوة بتكون صغيرة ومحدودة
- Rigidity
- "pill-rolling" tremor

■ The diagnosis is based on the triad

- Tremor
 - Rigidity
 - Bradykinesia
- Not unique for parkinsonism → exclude the other causes (e.g. drug abuse)
- Absence of toxic etiologies
 - Response to L-DOPA replacement therapy



Parkinson disease (PD)

- Morphology
 - Pallor of the substantia nigra
 - Lewy bodies
 - In some of the remaining neurons
 - Single or multiple cytoplasmic eosinophilic
 - Round to elongated inclusions
- loss of the black color of S. nigra

