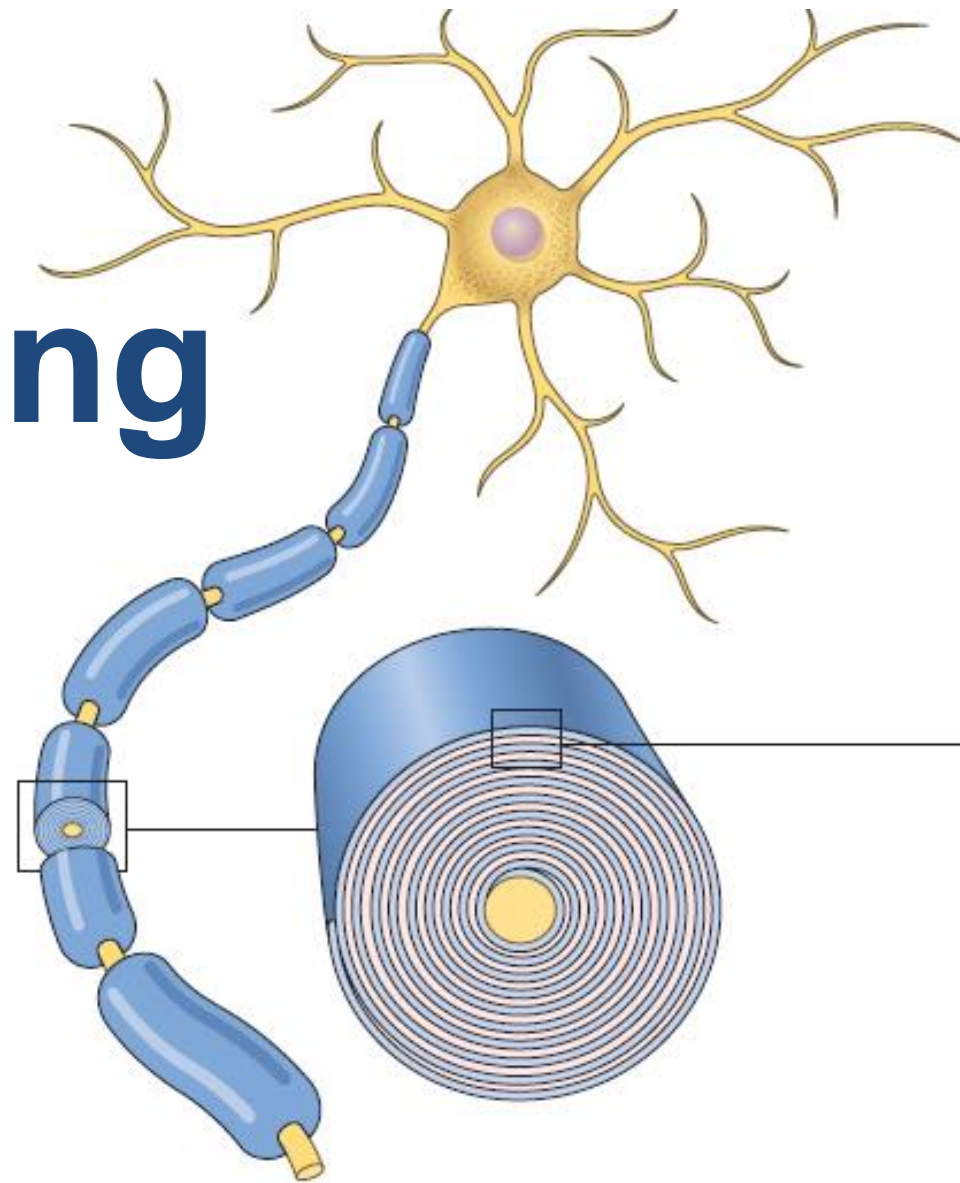




The CNS, II

Myelin increases the velocity and effectivity of signals conduction via nodes of Ranvier

Demyelinating diseases



Demyelinating diseases

- Acquired, preferential damage to myelin The primary target is myelin & oligodendrocytes
- Relative preservation of axons But it maybe affected in severe cases
- Initially effect on transmission of impulses along axons
- Determined in part by
 - The limited capacity of the CNS to regenerate the myelin
 - The degree of secondary damage to axons

They are the primary
determinants of the size
of the resulting defect

[Demyelinating diseases]

- Etiology

- Immune mediated destruction (MS)
- Infection (PML) Progressive multifocal leukoencephalopathy
- Inherited (leukodystrophies)
 - Affecting synthesis and turnover of myelin components

Multiple sclerosis (MS)

- Autoimmune demyelinating disorder
- Distinct episodes of neurologic deficits
 - Separated in time
 - Attributable to patchy white matter lesions that are separated in space بأماكن مختلفة
- The most common demyelinating disorder
 - 1/1000 in the US and EU

Also the gray matter can be affected but less commonly

- Most of nervous system disorders are well determined by the patient
 - Also it is continuous, stable and progressive غالباً المريض يعاني بشكل مستمر
- MS are quietly different
 - Each symptom is not related to the other
 - Patients face many relapses and remissions of the symptoms
 - Patients usually have general non specific symptoms of
 - Pins and needles
 - Numbness

- Hx of a case scenario of MS patient
 - e.g. 1 year of back having walking problems, urine incontinence...
 - e.g. 3 years of back having ocular problems
 - All of these problems the patient describes are often have improved by their own
 - i.e. Partial (but not complete) remission of some symptoms in MS occurs

[Multiple sclerosis (MS)]

- Any age
 - but rare in childhood and after 50
- W/M = 2/1
- Clinically relapsing and remitting episodes of variable duration
 - ↳ Usually is incomplete
- Neurologic deficits then gradual and partial recovery
- Relapses frequency tends to decrease over time
- But with steady neurologic deterioration

[Pathogenesis]

- Autoimmune response against myelin components
- Genetic factors
 - 15 fold in first degree *نوع الأقارب*
 - 150 fold in monozygotic twin
 - Strong association with HLA-DR
 - Additional association with IL-2 and IL-7 receptor, CKs/receptors genes
- Environmental factors
 - Geographic variation
 - Equator, sun/vit D??
*الذين الأقرب خط الاستواء
are more commonly affected*

[Pathogenesis]

■ Immune mechanisms

- Initiated by Th1 and Th17 cells →
- Reaction against myelin
- Secrete cytokines
- Th1 secrete INF- γ , activates macrophages
- Th17; recruitment of leukocytes,
- Demyelination by these activated leukocytes and their injurious products

This indicates

- Cell-mediated immune response, or
- Type of hypersensitivity reaction

[Pathogenesis]

- Immune mechanisms

- The infiltrate in plaques

- CD4, CD8 and macrophages

- How the autoimmune reaction is initiated??

- Viral infection?? *May trigger the events*

- Therapy

- Modulation or inhibition of T-cell responses

- Blocking of the recruitment of T-cells to the brain

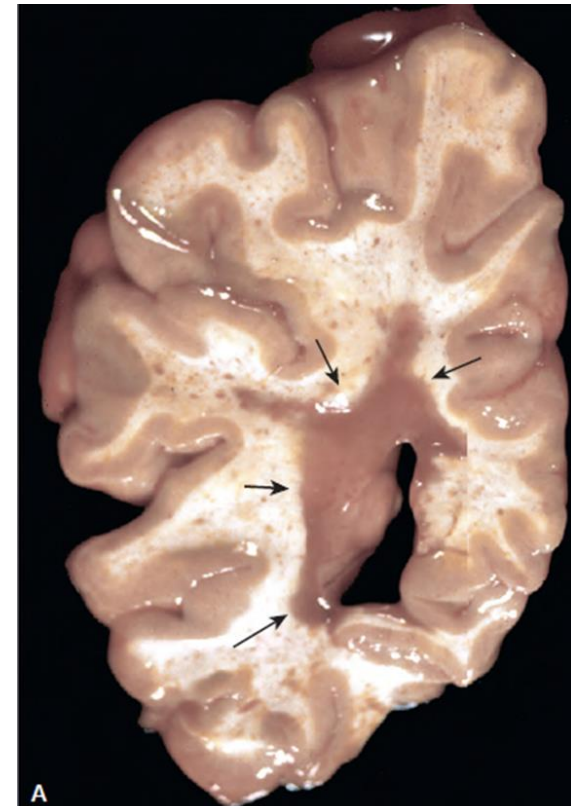
- Depletion of B-cell Igs ????

Treatments that target B-cells are useful → this ensures that B-cells have role in the pathogenesis of the disease

[Morphology]

- A white matter disease
- The lesion
 - Is ^{Hard} firmer than the surrounding white matter “sclerosis”
 - Well circumscribed
 - Depressed
 - Glassy
 - Irregularly shaped plaques
- The area of demyelination
 - Sharply defined borders

ينتج عن إصابة تسمى مرض
Results in multiple sclerotic plaques



- Active plaques

- Ongoing inflammation within it

- Inactive plaques

- Are in remission phase
- Decreased inflammation within it due to the regulatory lymphocytes
- The end result is gliosis 'gliosis is sclerosis of brain tissue'

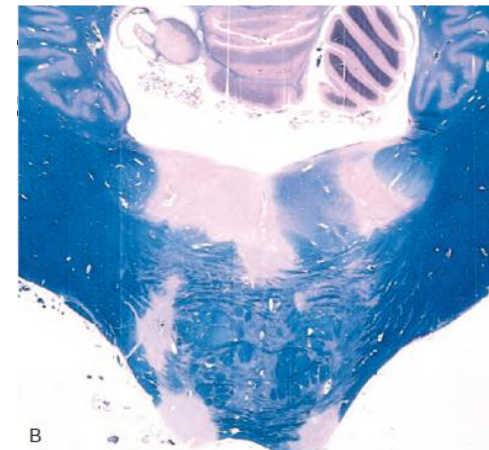
[Morphology]

- Localization Commonly
 - Adjacent to the lateral ventricles
 - In the C. callosum
 - Optic nerves and chiasm
 - Brainstem
 - Ascending and descending fiber tracts
 - Cerebellum, and spinal cord
- Plaques can extend into gray matter

[Morphology]

- Ongoing myelin break-down
- Associated with abundant foamy macrophages *Are macrophages engulfing myelin (which is lipid)*
- with lymphocytes as perivascular cuffing at the outer edge of the lesion
- Active lesions are often centered on small veins; myelin is completely absent
- Axons are relatively preserved

Myelin is stained blue by luxol stain
Axons are stained by Neurofilament (NF) protein
CT is stained blue by trichrome stain



[Morphology]

- In time reactive changes of the astrocytes
- As lesion become quiescent; inflammatory cells slowly disappear
- Inactive plaque
 - No macrophages
 - Little to no myelin
 - Reduced oligos *Oligodendrocytes*
 - Prominent reactive gliosis
 - Greatly diminished axons in old gliotic plaques



Diseases of Peripheral Nerves

[Types of injury]

■ Axonal neuropathy

○ Primary damage of axons

○ Wallerian degeneration

نظرية لها شروط معينة
وصعب تطبيقها

تجارب على الحيوانات يعني بنقطع nerve وبنشوف شو هيجصل

■ Sequence of events

→ After cutting the nerve:

■ Traumatic neuroma

→ Also called amputation neuroma

- Due to amputation of a part of the body
- Non neoplastic
- Forms as a result of the repair attempts of the axons
- Axons **intermingled** together along with schwann cells and other neuronal elements

• Distal part

- **Degenerates**

• Proximal part

- **Starts to grow to replace the distal**

[Types of injury]

- Demyelinating neuropathy
 - Primary damage targeting myelin and Schwann cells
 - Relatively preserved axons
 - Random degeneration
 - Repair attempts by schwann cells : Such as oligos
: But never ever become like the original morphology
 - Shorter and thinner than original internodes
 - Electrophysiologic hallmark is slowed nerve conduction velocity due to loss of myelin

[Types of injury]

- Cell bodies (perikaryon) degeneration Neuronopathies
 - Axon degeneration secondary to destruction of neuron Cell bodies
 - H. zoster
 - Platinum compounds Chemotherapeutic agents

Anatomic patterns of peripheral neuropathies

- Mononeuropathies

- Single nerve and distribution
- Infection and trauma

- Polyneuropathies

- Multiple nerves
- Usually symmetric Left as right
- Axons are affected in length dependent fashion

Anatomic patterns of peripheral neuropathies

- Mononeuritis multiplex
 - Individual nerves in a haphazard fashion
 - Vasculitis
- Polyradiculoneuropathies
 - Affect ^{In the spinal cord} nerve roots as well as peripheral nerves → The problem is usually concentrated in the roots
 - Leading to diffuse symmetric symptoms
 - In proximal and distal parts of the body → Equally affected

[Specific peripheral neuropathies]

- Clinically
 - Numbness
 - “pins and needles” sensation
 - Weakness; distal

[Specific peripheral neuropathies]

- Types
 - Inflammatory
 - Infectious
 - Metabolic
 - Toxic
 - Trauma
 - Paraneoplastic
 - Genetic

Inflammatory neuropathies: Guillain-Barré Syndrome

Is the counterpart of MS in peripheral nervous system

- Immunologically mediated
- Acute inflammatory demyelinating polyneuropathy
- May lead to respiratory paralysis
- 1/100000/year
- Weakness from distal to proximal limbs “ascending paralysis”
- Inflammation and demyelination of spinal nerve roots and peripheral nerves = radiculoneuropathy

Guillain-Barrè Syndrome

■ Pathogenesis

- Acute onset, immune mediated, demyelinating neuropathy
- 2/3 preceded by influenza like illness
- As well as association with
 - C. jejuni, CMV, EBV, and M. pneumonia
 - Vaccination
- No microorganism in the nerves
- Experimentally role of lymphocytes, macrophages and Abs

· Infections are triggering agents and contribute to the disease indirectly
○ I.e. You will not see the infectious agents in the nerves ;)

Guillain-Barrè Syndrome

- Morphology

- Inflammation of peripheral nerves
 - Perivenular & endoneurial infiltration
 - Lymphocytes, macrophages and few plasma cells
 - Segmental demyelination
 - Damage to axons is also seen (in severe conditions)
 - Inflammation is more prominent close to the nerve roots
- Radiculoneuropathy

Infectious neuropathies: Varicella-zoster virus

- Common
- Latent infection of chickenpox in sensory ganglia
- Reactivation and transport to dermatomes (shingles)
 - Decreased cell mediated immunity??
- Neuronal death with abundant mononuclear infiltrate
- Degeneration of axons

- When reactivated in the ganglia it will be transported by the cell processes toward the skin of the related dermatome
 - Then it infects keratinocytes resulting in the symptoms



[Metabolic neuropathies: DM]

- DM is the most common cause of peripheral neuropathy
- Overall 50% of Diabetic patients
- Mostly ascending distal symmetric sensorimotor poly neuropathy

[Metabolic neuropathies: DM]

■ Pathogenesis

- Complex
 - Damage to both axons and Schwann cells
 - Non enzymatic glycosylation of proteins, lipids and nucleic acids
 - Activation of inflammatory signaling
 - Depletion of NADPH Antioxidant
 - Injury by free radicals
 - Or secondary damage due to vascular ischemia
- DM usually result in vascular pathology → ischemia → damage to nerves

[Metabolic neuropathies: DM]

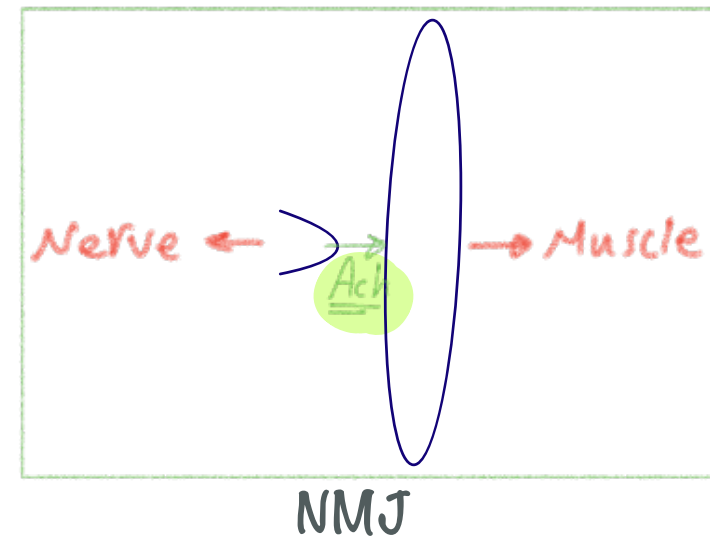
- Morphology
 - Axonal neuropathy
 - Reduced number of axons
 - Degenerating myelin sheaths
 - Regenerative axonal clusters *Amputation neuroma*
 - Thickening hyalinization of endoneurial arterioles



Diseases of Neuromuscular Junctions

Diseases of the NMJ

- Physiology When the nerve reaches the striated muscle it branches off into multiple branches; each of which ends with a bulbous swelling that synapses with sarcolemmal membrane (membrane of a myocyte)
- Painless weakness and fatigue
- Autoantibodies



[Myasthenia gravis]

- Ab mediated disease of the NMJ
- Autoimmune
- Auto Abs against ACh receptors
- 150-200/1000000
- Bimodal age distribution

[Myasthenia gravis]

- Pathogenesis

- ACh Rs autoAbs

- Pathogenic
 - Passive transfer to animals
 - Improvement by decreasing these Abs
 - Leads to aggregation and destruction of the receptors
 - Damage to postsynaptic membrane through complement fixation
 - No response to ACh

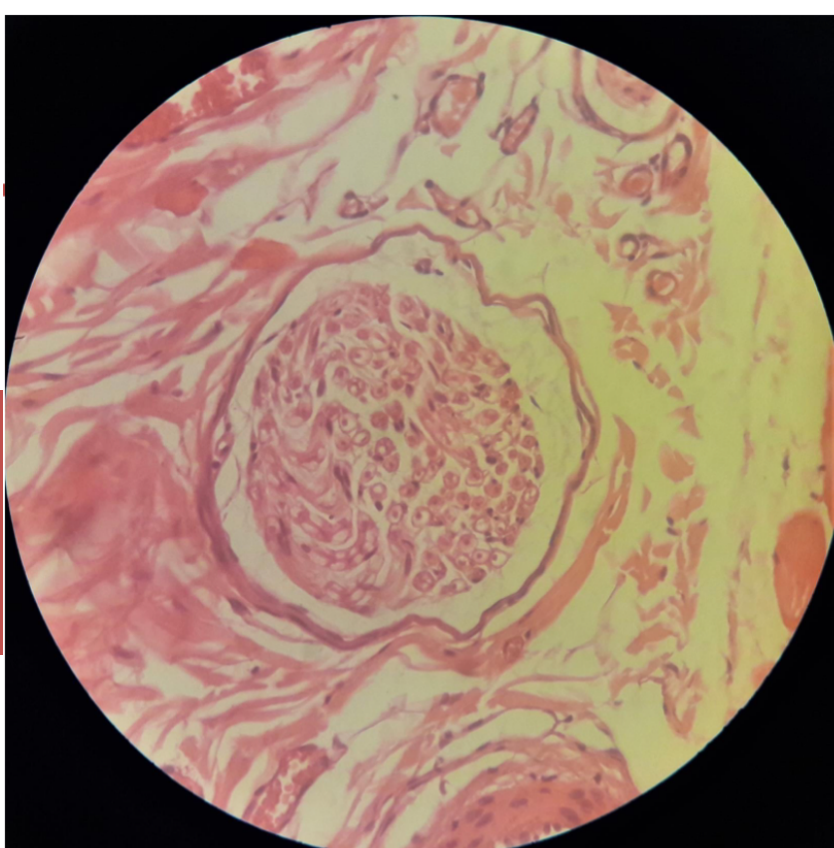
[Myasthenia gravis]

- Pathogenesis

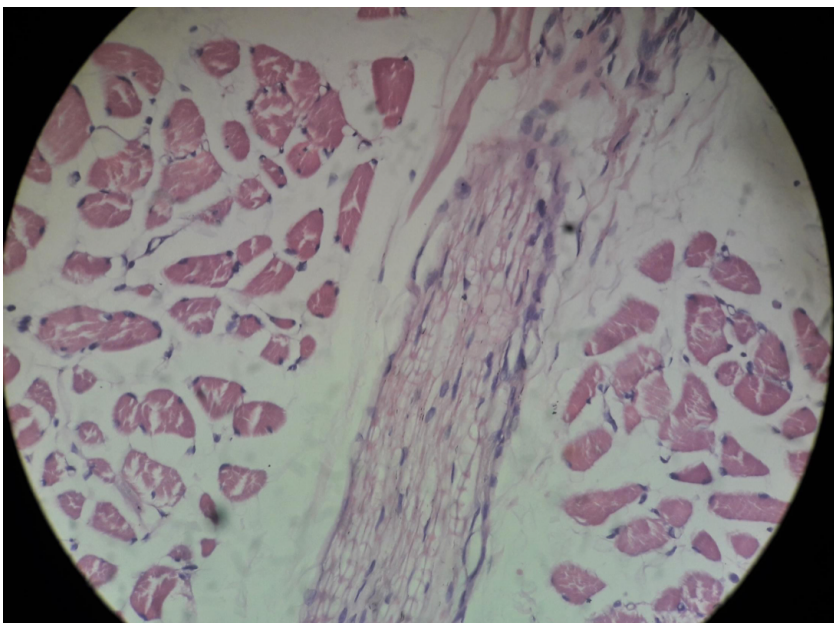
- Strong association with thymic abnormalities
- 10% thymoma
- 30% thymic hyperplasia
- Promoting autoimmunity



Peripheral Nerve Sheath Tumors ‘PNSTs’



- The nerve is surrounded by a space 'perineural space', beyond this space, a perineural connective tissue exists
- **Note**
 - Tumors usually metastasize by lymphovascular invasion
 - There is another way of metastasis of tumors which is perineural invasion or metastasis through perineural space
 - Most commonly in prostatic carcinoma, mucoepidermoid carcinoma of salivary glands, and some of breast cancers



- Axons are surrounded by clear areas on each side which is the myelin
- Myelin dissolves in the solutions we use to stain nerves producing a vacuum

[PNSTs]

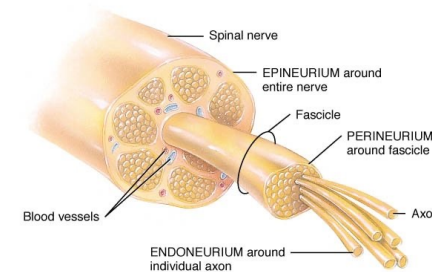
- Most reveal Schwann cell differentiation
- Rarely perineurial cell differentiation
- Common types

- Schwannoma
- Neurofibroma
- MPNST

They all have the same origin & differentiation

- They originate from Schwann cells

The cells of perineurium



Malignant PNST

- Abrupt transition between central and peripheral myelin

- PNSTs may arise within the dura

مجرد ما اخرج من CNS للـ PNS يصير كـ Schwann cells
هنا الميولينة عنده myelination بدل الـ Oligos

وهنا الانسجة مش دائماً بيكون خارج الـ CNS
يعني ممكن يكون في الـ Schwann cells جوا CNS مش تدا ممكن نادق PNST في الـ dura

[PNSTs]

- Familial tumor syndromes

- Hereditary
- Tendency to form more than one tumor
- Earlier age of onset

- Unique features

- Association with common familial tumor syndromes

- NF1 *Very common*
- NF2
- Schwannomatosis

- MPNSTs in the context of NF1 are thought to arise through malignant transformation of preexisting neurofibroma (unusual for soft tissue tumor)

The majority of malignant STTs and other malignant tumors arise de novo; not via transformation from benign to malignant

Benign ↖

Schwannomas

- Arise directly from nerves
 - Schwann cell differentiation
 - Hereditary
 - A component of NF2
 - Sporadic *The majority*
 - Commonly associated with inactivation of NF2 gene
 - Thus loss of function of merlin
 - Component of the cytoskeleton
 - The specific protein of NF2
 - A consistent finding of all Schwannoma
 - All Schwannomas have NF2 mutations which result in loss of function of Merlin
- Functions of Merlin ■ Participates in control of cell shape, growth and adhesion

Morphology

Gross

- Well-defined encapsulated mass surrounded by well-developed capsule
- Cut surface
 - Gray white
 - Some sort of fibrillary texture
 - May has a myxoid background

Microscopic

Antoni A and B

- Antoni A
 - The dense eosinophilic cellular area
 - Large nodule consist of multiple verocay bodies
- Antoni B
 - The hypocellular area

No importance in prognosis or treatment

Verocay bodies

Resulting structures with central “nuclear-free zones” ramified by palisading nuclei

Morphology of Schwann cell

Schwann cells are characterized by the presence of a spindled elongated nucleus with a wavy or buckled shape ‘characteristic’

No axons

EM

IHC

Positive for S100 protein

- Capsule
- The borders are well defined not infiltrative
- Nodularity
- Unique arrangement of nuclei
 - As if you look at a swarm of fish
- Characterized by dual morphology
 - Cellular parts (nodular parts) (Antoni A)
 - Hypocellular parts (Antoni B)

[Morphology]

- Degenerative changes
- May recur locally If incompletely resected
- Extremely rare malignant transformation

- Enlargement of nuclei, Irregular shaped, Bizarre morphology
 - Those all are characters of nuclear atypia that occurs in malignant tumors, but Schwannomas are benign so how!!!
 - We should note that
 - atypia alone is not enough to diagnose a tumor as a malignant
 - this atypia of schwannoma is not associated with increased mitotic activity
 - no increased mitosis = no malignancy
 - so by this mean we differentiate benign Schwannomas from MPNSTs

Localization

Everywhere in the body

Misnomer

- Acoustic neuroma
- Within the dura, sensory nerves are preferred
 - Trigeminal nerve and dorsal roots
- Extradural
 - Association with large nerve trunks
 - Soft tissue without identifiable nerve

We cannot identify the nerve from which the Schwannoma arises

- Bilateral schwannoma related to CN VIII
- Seen in NF2
- Double misnomer
 - Acoustic (Wrong) → It originates from the vestibular part of the CN VIII not from acoustic
 - Neuroma (Wrong) → It originates from Schwann cells not from neural cells

Neurofibromas

The tumor is composed of
Schwann cells and other cells

■ More heterogenous composition than schwannoma

- Schwann cells
- Perineurial like cells
- Fibroblasts
- Mast cells
- CD34+ spindle cells

The neoplastic cells in NF

The tumor is composed
of Schwann cells only

Other components
of the NF but are
non-neoplastic

- Although these cells are non-neoplastic, they are not innocent
- They may secrete substances that induce proliferation of Schwann cells

Neurofibromas

■ Presentation

- Sporadic
- NF1 associated *Hereditary*

■ Types of growth pattern

- Superficial cutaneous neurofibromas *Well-defined mass in the skin*

Most commonly associated with sporadic pattern

Single or multiple

Most commonly associated with hereditary pattern (NF1 associated)

- Diffuse neurofibromas

- No well-defined mass
- Only thickening or hardness of the skin occurs

Most commonly associated with hereditary pattern (NF1 associated)

Plaque like

- Plexiform neurofibroma

- Network or bag of worm
- Pathognomic for NF1 ;)

- Tumor suppressor gene
- RAS system
 - Has GTPase activity
 - GTPase inactivates the RAS after the signal has removed
 - GTPase Activating Proteins (GAPs)
 - Activate GTPase to keep the cell under tight control and suppress overgrowth
- NF1 encodes one of the GAPs ;)
- So play a role in suppression of tumors
- If has lost its function, overgrowth and tumor occur

[Pathogenesis]

- Complete loss of NF1 in schwann cells ... neoplastic
- Role in carcinogenesis *NF1 gene encodes one of the GAPs which is neurofibromin*
- **Haploinsufficiency** for NF1 in other cells also may contribute to growth

Loss of function of only one allele not the 2 alleles as in Schwann cells

- Hypersensitive mast cells to KIT ligand produced by schwann cells
 - May be targeted by **inhibitors of KIT RTK** Therapy
- **Secreting factors stimulate schwann cell growth**

Schwann cells secrete KIT ligand → Mast cells response to it by secreting factors that stimulate Schwann cell growth

[Pathogenesis]

- Plexiform NFs and dermal NFs arise from different neural crest precursors
- Malignant transformation
 - Usually in plexiform NFs Most common
 - Some times in diffuse type
 - The overall incidence of MPNST in NF1 patients 5-10%
 - Higher risk in those with large number of plexiform NFs and large deletions in the NF1 gene

As the number of benign NFs increase, the potential of MPNST occurrence increases

[Morphology]

■ Localized cutaneous neurofibroma

- Gross
- Localization
- Hypocellular loose collagen
- Cellular composition
- Entrapment of adnexae

In the dermis and subcutaneous fatty tissue

- The tumor is composed of Schwann cells and other cells
- In contrast to Schwannomas, it is not encapsulated

- Infiltrative in the dermis and SC tissue
 - Skin appendages are seen trapped inside the tumor
 - Skin appendages = eccrine sweat glands, hair follicles...

■ Diffuse neurofibroma

- Different pattern
- Large sizes
- Meissner corpuscles

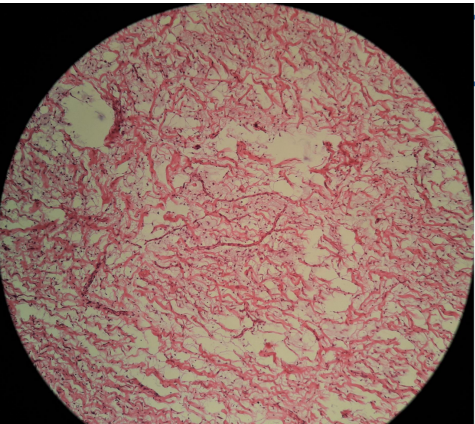
Tends to form Meissner corpuscles

[Morphology]

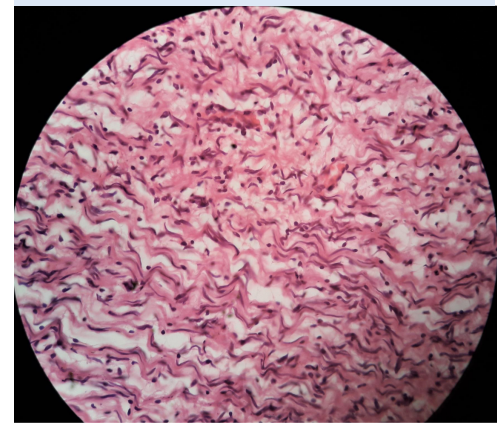
■ Plexiform neurofibroma

- Within and expand the nerve This makes the nerves tortuous
- Entrapping associated axons In contrast to Schwannomas
- Perineurial layer is preserved
 - Isolates it from the surrounding
 - Not as other types of neurofibroma
- Giving encapsulated appearance
- “bag of worms” appearance
- Myxoid/fibrous stroma
- “shredded carrot” like collagen

شبه الجزر المقشر



Wavy appearance of Schwann cells



[Malignant PNSTs “MPNSTs”]

- Mostly 85% are high grade tumors
- 50% arise NF1 patients
 - Transformation from Plexiform NF
- de novo sporadic cases
- Most associated with large nerves in the chest, abdomen, pelvis, ...
- Complex chromosomal aberrations

[Morphology]

- Invasive, poorly demarcated
- Fascicles of spindle cells
- “Marbleized”, variation in cellularity
- Mitosis, necrosis and anaplasia
- Divergent differentiation
 - “Triton tumor”
- Clues to diagnosis
 - NF1, Relation to nerve, Preexisting neurofibroma

· PNSTs may differentiate into cartilage, bone, striated muscle (rhabdomyocytes)...

○ Rhabdomyoplastic differentiation is the most common and is called triton tumor

شبه ابرخام

[Von recklinghausen disease Neurofibromatosis type I]

- Autosomal dominant
- 1/3000
- Non neoplastic manifestations
 - Intellectual disability
 - Seizures
 - Skeletal defects
 - Pigmented nodules of the iris “Lisch nodules”
 - “café au lait” spots



[Neurofibromatosis type I]

- Tumors Neoplastic manifestations
 - NFs of all types
 - MPNSTs 5-10% of cases
 - Gliomas of optic nerve
 - Hamartomas
 - Pheo s Pheochromocytoma

Neurofibromatosis type I

- Loss of function mutation of NF1 gene
 - 17q11.2
 - Mechanism of action
- High penetrance but variable expressivity
 - Some express subtle features
 - Some show disease restricted to certain body parts “mosaicism”
 - Some with severe disease
 - Large chromosomal deletions

بيتم توارثها بشكل كبير يعني لو حدا عنده ال syndrome غالباً رح يعطيها لاولاده
لكن اعراض المرض عنده وعند اولاده ممكن تختلف يعني ممكن حدا يكون عنده severe وحدا ثاني لا

[Neurofibromatosis type II]

- Autosomal dominant
- NF2 gene on 22q12
 - Commonly mutated in sporadic meningiomas and schwannomas
 - “merlin”
 - Role
- 1/40000-50000 *Lower frequency than NF1*

Neurofibromatosis type II

■ Tumors

- Bilateral 8th nerve schwannomas *Acoustic neuroma*
- Multiple *meningiomas* and *ependymomas* of spinal cord

■ Non neoplastic manifestations

- *Schwannosis* *Extensions or ingrowth of Schwann cells especially in the back area in front of spinal cord that may enter the spinal cord*
- *Meningioangiomas*
 - Proliferation of meningeal cells along with BVs
 - May invade the brain (but not malignant)
- *Glial hamartia* *Areas of Neuroglial cells proliferation in the cerebral cortex*

✕ ■ Schwannomas in other syndromes

- Schwannomatosis
- Carney complex