وقل رب زدني علماً

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PERIPHERAL NERVOUS SYSTEM

SUBJECT : Pathology-TABLE

LEC NO. : 4

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PNS

Pathology Lecture 4

Disorders of Peripheral Nerves

Patterns of Peripheral Nerve Injury is Subclassified as axonal or demyelinating (many diseases show mixed features)

Patterns of Peripheral Nerve Injury	
Axonal neuropathies (Wallerian degeneration)	- Caused by insults that directly injure the axon - The entire distal portion of an affected axon degenerates - Associated with secondary myelin loss -Regeneration takes place through axonal regrowth and subsequent remyelination of the distal axon
	MORPHOLOGY: Decrease in the density of axons, which correlates with a decrease in the signal strength or amplitude of nerve impulses
Demyelinating neuropathies	- Damage to Schwann cells or myelin with relative axonal sparing, resulting in abnormally slow nerve conduction velocities - Demyelination typically occurs discontinuously, affecting individual internodes along the length of an axon in a random distribution - This process is termed segmental demyelination - Remyelination to take place, but the new internodes are shorter and have thinner myelin sheaths, +/- onion bulbs
	MORPHOLOGY: -Show a relatively normal density of axons with abnormally thin myelin sheaths and short internodes

Anatomic patterns of Peripheral Neuropathies	
1. Polyneuropathies	-Usually affects nerves in a symmetric, length-dependent fashion - Axonal loss is typically more pronounced in the distal segments of the longest nerves (BILATERAL) -Patients commonly present with loss of sensation and paresthesias that start in the toes and spread upward. By the time the sensory changes reach the level of the knees, the hands are also affected, resulting in a picture described as "stocking-and-glove" distribution -Often encountered with toxic and metabolic (e.x: DM) damage -DAMAGE TO TERMINAL BRANCHES OF MULTIPLE NERVES -RESULT IN SYMMETRICAL, DISTAL DISTRIBUTION
2. Mononeuritis multiplex	-The damage randomly affects individual nerves, resulting (for example) in a right radial nerve palsy and wrist drop and, at a separate point in time, a left foot drop - Often caused by vasculitis -DAMAGE TO >= 2 PERIPHERAL NERVES -RESULT IN ASYMMETRICAL DISTRIBUTION
3. Simple mononeuropathy	-Only involves a single nerve -Most commonly with traumatic injury, entrapment (e.x: Carpal tunnel syndrome) or certain infections DAMGE TO A SINGLE PERIPHERAL NERVE

SYMPTOMS of Peripheral Neuropathy

Sensory	• Paresthesia (tingling, pins & needles, prickling, burning) • Numbness • Abnormal degrees and types of sensation
Motor	• Weakness • Wasting • Muscle twitching (fasciculation)

General Causes for Axonal & Demyelinating neuropathies

- **Nutritional and metabolic** (DM, Uremia, Vitamin deficiencies) -**Toxic** (Drugs, Toxins, Chemicals)

-**Vasculopathic** (Vasculitis, Amyloidosis) -**Inflammatory** (ACUTE: Guillain-Barre syndrome, CHRONIC)

-**Infections** -**Inherited** -**Trauma**

PERIPHERAL NEUROPATHY

Diabetic Peripheral Neuropathy

Diabetes is the most common cause of peripheral neuropathy

- NEUROPATHIES INCLUDE **SEVERAL FORMS:**

• **Distal symmetric sensorimotor polyneuropathy:** is the most common form of diabetic neuropathy (Sensory axons are more severely affected than motor axons/ paresthesias and numbness)

• **Autonomic neuropathy:** changes in bowel, bladder, cardiac, or sexual function.

• **Lumbosacral radiculopathy:** manifests with asymmetric pain that can progress to lower extremity weakness and muscle atrophy

THE PATHOGENESIS:

- Accumulation of advanced glycosylation
- Increased levels of ROS
- Microvascular changes

Toxic, Vasculitic, and Inherited Forms of Peripheral Neuropathy

Drugs and environmental toxins	- Interfere with axonal transport or cytoskeletal function - The longest axons are most susceptible; hence, symptoms appear first and are most pronounced in the distal extremities
Systemic vasculitis	-Including polyarteritis nodosa, Churg-Strauss syndrome, and polyangiitis with granulomatosis
Inherited diseases (LATE PRESENTATION)	- Heterogeneous but relatively common - Can be demyelinating or axonal - Many manifest in adulthood and follow a slowly progressive course - The most common causes are mutations in the genes encoding myelin-associated proteins

Guillain-Barré Syndrome

- A rapidly progressive acute demyelinating disorder affecting motor axons, resulting in ascending weakness
- Sensory involvement is usually much less striking than motor dysfunction
- Can lead to death from failure of respiratory muscles within days of onset of symptoms
- It is one of the most common life-threatening diseases of the peripheral nervous system
- Appears to be triggered by an infection or vaccination that breaks down self-tolerance, thereby leading to an autoimmune response
- Associated infectious agents include Campylobacter jejuni, EBV, CMV, HIV
- Both humoral and cellular immune responses are believed to play a role in the disease process
- The injury is most extensive in the nerve roots and proximal nerve segments
- Patients who survive the initial acute phase of the disease usually recover with time

HISTOLOGY: -

Segmental demyelination with peripheral nerve mononuclear cell infiltrates rich in macrophages

PNS Tumors

- Usually occur in adults and include both benign and malignant variants.
- In most, the neoplastic cells show evidence of Schwann cell differentiation
- In addition to arising along the peripheral course of nerve, these tumors can arise within the confines of the dura causing changes in adjacent brain or spinal cord

Tumors of peripheral nervous system

1. Schwannomas

- Benign encapsulated tumors that may occur in soft tissues, internal organs, or spinal nerve roots
- The most commonly affected cranial nerve is the vestibular portion of the eighth nerve within the cerebellopontine angle
- Tumors arising in a nerve root or the vestibular nerve may be associated with symptoms related to nerve root compression, such as hearing loss in vestibular schwannomas
- Most schwannomas are sporadic, but about 10% are associated with familial neurofibromatosis type 2 (NF2)

MORPHOLOGY: Most are circumscribed masses abutting the adjacent nerve

MICROSCOPICALLY: They are comprised of a uniform proliferation of neoplastic Schwann cells

- Show an admixture of dense (Antoni A) and loose hypocellular areas (Antoni B)
- In Antoni A areas, bland spindle cells are arranged into intersecting fascicles with nuclear palisading, resulting in alternating bands of nuclear and anuclear areas called Verocay bodies
- In Antoni B areas, the spindle cells are spread apart by a myxoid extracellular matrix (MYXOID BACKGROUND)
- Axons are excluded from the tumor
- Thick-walled hyalinized vessels often are present
- Tumor cells are positive for S100 by IHC

2. Neurofibromas

- Benign peripheral nerve sheath tumors
- THREE IMPORTANT SUBTYPES ARE RECOGNIZED:

▪Localized cutaneous neurofibromas: superficial nodular tumors. These occur either as solitary sporadic lesions or often as multiple lesions in (NF1)

▪Plexiform neurofibromas grow diffusely within the confines of a nerve or nerve plexus (Surgical enucleation of such lesions is, therefore, difficult) They are virtually pathognomonic for NF1 and are associated with a small but real risk of malignant transformation

▪Diffuse neurofibromas: infiltrative proliferations that can take the form of large, disfiguring subcutaneous masses. These also are often associated with NF1

MORPHOLOGY: Not encapsulated - Appear circumscribed, as in localized cutaneous neurofibromas, or may exhibit a diffusely infiltrative growth pattern

MICROSCOPICALLY:

- The neoplastic Schwann cells are mixed with other cells, including mast cells, fibroblast-like cells, and perineurial-like cells
- The background stroma contains loose wavy collagen bundles but also can be myxoid or can contain dense collagen (CARROT SHAVING APPEARANCE)
- Plexiform neurofibromas involve multiple fascicles of individual affected nerves
- Diffuse neurofibromas show an extensive infiltrative pattern of growth within the dermis and subcutis of the skin

3. Malignant Peripheral Nerve Sheath Tumors

- Seen in adults and shows evidence of Schwann cell derivation and sometimes a clear origin from a peripheral nerve
- May arise de novo or from transformation of a neurofibroma, usually of the plexiform type
- About one-half of such tumors arise in patients with NF1, and 3% to 10% of all patients with NF1 develop a malignant peripheral nerve sheath tumor during their lifetimes
- Poorly defined masses with frequent infiltration along the axis of the parent nerve

MICROSCOPICALLY:
- Highly cellular and exhibit features of overt malignancy, including anaplasia, necrosis, infiltrative growth pattern, pleomorphism, and high proliferative activity

Traumatic Neuroma

- A nonneoplastic proliferation associated with a previous injury leading to transection of a peripheral nerve
- Such injuries activate a regenerative program characterized by sprouting and elongation of processes from the proximal axonal stump
- With severe injuries that disrupt the perineurial sheath, these new processes may "miss" their target, the distal end of the transected nerve. The misguided elongating axonal processes can induce a reactive proliferation of Schwann cells, leading to the formation of a painful localized nodule CONSISTING OF a haphazard mixture of axons, Schwann cells, and connective tissue

Familial Tumor Syndromes

Neurofibromatosis Type 1 (NF1)

An autosomal dominant disorder caused by mutations in the tumor suppressor neurofibromin (ON CHROMOSOME 17)

- Associated tumors include neurofibromas of all three main types, malignant peripheral nerve sheath tumors, "optic gliomas," and other glial tumors

- In addition, patients with NF1 exhibit learning disabilities, seizures, skeletal abnormalities, vascular abnormalities with arterial stenoses, pigmented nodules of the iris (Lisch nodules), and pigmented skin lesions (axillary freckling and café-au-lait spots) in various degrees.

Neurofibromatosis Type 2 (NF2)

- AD, NF2 affected patients carry a dominant loss of function mutation of the Merlin gene (ON CHROMOSOME 22)

- NF2 patients are at risk of developing multiple schwannomas, meningiomas, and ependymomas

- The presence of bilateral vestibular schwannomas is a hallmark of NF2.