

Outlines

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- > Infectious Neuropathies
 - > VZV
- > Metabolic Neuropathies
 - > DM

Diseases of the NMJ

Myasthenia Gravis



Demyelinating Diseases

- > Acquired conditions characterized by preferential damage to Myelin & Oligodendrocytes, with relative preservation of axons in most cases.
 - > May be affected in severe cases.
 - > Responsible for Myelin synthesis in CNS neurons.
- > Initially affecting transmission of electrical impulses along axons.
 - > Affects the velocity of action potential conduction.
- > The degree of the disease determined by:
 - 1) The limited capacity of CNS to regenerate normal myelin.
 - 2) The degree of damage to axons that occurs as the disease runs its course.
- > May be caused by:
 - 1) Immune-mediated destruction of myelin (Autoimmune Dz).
 - > As in Multiple Sclerosis [MS].
 - 2) Infections > Mainly Viral.
 - > As in Progressive Multifocal Leukoencephalopathy [PML].
 - 3) Genetic defects > Affect genes involved in synthesis or turnover of myelin components.
 - > Termed Leukodystrophies.
 - "Degradation"

Multiple Sclerosis (MS)

- > Autoimmune demyelinating Dz characterized by distinct episodes of neurologic deficits that are separated in time & space.
 - > w/ partial improvement of symptoms.
 - > Symptoms are NOT related in site.
 - أَنوَ أَمَاكِن الـ Symptoms ما إِلِها عِلَاقَة بِيَعْضُها.
 - > Attributable to patchy white matter lesions that are separated in space.
 - > Certain areas more frequently affected such as around Lateral ventricles & Corpus callosum.
 - > Even Spinal cord & Brainstem could be affected.
 - > The lesions may extend into Gray matter.
- > M/C of Demyelinating disorders.
 - > 1/1000 persons in US & Europe.
- > All ages may be affected.
 - > M/C b/w 20-40 years old.
 - > Rare in childhood & after 50.
- > Women are affected twice as often as are men.
 - > Female : Male > 2:1
- > Presents clinically in the form of relapsing & remitting episodes of variable duration.
 - > Marked by neurologic defects >> followed by gradual & partial recovery of neurologic function.
 - > i.e most often ends by incomplete remission of symptoms.
 - > The frequency of relapses tends to decrease over time.
 - > but there is a steady neurologic deterioration in most affected individuals.
 - أَنوَ عَلَي المَدَى الطَوِيل، الـ Deficiet يَبْزِدَاد سَوَاءً.

Pathogenesis

- > Autoimmune response against myelin components (self Ag).
- > Involves both genetic & environmental factors.
 - > The environmental factors will trigger the defective genes.
 - > **Genetic Factors:**
 - > The incidence of MS is 15-fold higher when the Dz is present in a first-degree relative.
 - > roughly 150-fold higher w/ an affected monozygotic twin.
 - > There is a strong association w/ certain types of **HLA-DR**.
الملي بتخلي ال APC تتعرف عال Ag، هل هو self or non-self Ag
 - > Additional associations w/ IL-2 & IL-7 receptor genes & CKs receptors genes.
 - > **Environmental Factors:**
 - > Geographic variation in prevalence of MS.
 - > w/ a higher number of cases diagnosed away from the equator.
 - > may be related to ↓ vitamin D (an immune system modulator) in people who are NOT exposed to sunlight during winter.
 - > The disease initiated by **Th1 & Th17** cells that react against myelin Ags & secrete cytokines.
 - > Cell-mediated immune response >> Type IV Hypersensitivity.
 - > Th1 cells secrete IFN-γ >> activates macrophages.
 - > Th17 cells promote the recruitment of leukocytes.
 - > results in amplification of the immune response.
 - > The demyelination caused by these activated leukocytes & their **injurious products**.
 - > As Oxygen specieses (Free radicals) >> highly destructive elements >> destruct myelin.
 - > The genetic defects are responsible on initiation of all these processes.
 - > Elements of this inflammatory process form **MS plaques** which are haphazardly arranged among brain white matter.
 - > Consists of T cells (mainly CD4+, some CD8+) & macrophages.
 - > How the autoimmune reaction is initiated is NOT understood.
 - > a role of viral infection (e.g., EBV) may be involved.
 - > Therapies include:
 - > Modulation or inhibition of T-cell responses.
 - > Blocking the recruitment of T cells to the brain.
 - > Agents that deplete B cells & ↓ Ig production.

MORPHOLOGY

> Gross Morphology:

- > White matter Dz.
 - > MS plaques haphazardly arranged among brain white matter.
- > The lesion is firmer (harder) than the surrounding white matter.
< ومن هان جاءت التسمية، Sclerosis. لأنه في أكثر من Lesion عادةً.
- > The lesion is well circumscribed, depressed, glassy, irregularly shaped plaques.
 - > The area of demyelination often has sharply defined borders.
 - > Variable in size few mms to several cms.

- > Plaques commonly occur adjacent to Lateral ventricles.
 - > Also frequent in corpus callosum, optic nerves & chiasm.
 - > May occur in brainstem, ascending & descending fiber tracts, cerebellum & spinal cord.
- > Plaques can extend into Gray matter.

> Microscopic Morphology:

> In an active plaque:

- > There is ongoing myelin breakdown associated w/ abundant foamy macrophages.
 - > engulf myelin which is lipid.
- > Lymphocytes also present as perivascular cuffs (تشايا) at the outer edge of the lesion.
- > Active lesions often centered on (around) small veins.
- > Myelin is usually completely absent, but axons are relatively preserved.
 - > Myelin stained blue by "Luxol fast blue stain".
 - > Completely destroyed & engulfed by macrophages >> so we won't see the blue color of myelin.
- > IHC against Neurofilament (NF) Protein used to show the neuron & its axon.
- > In time, astrocytes undergo reactive changes to form a network of processes "Gliosis" >> Scar tissue of brain.
- > As lesions become quiescent (ساکنة) >> the inflammatory cells slowly disappear.

> In an inactive plaque:

- > No macrophages, Little to no myelin, Reduced oligodendrocytes.
 - > Destroyed by the immune response.
- > Oligodendrocytes proliferate again & form new myelin > remission of the Dz.
 - > do NOT have the same quantity & quality.
- > Prominent reactive gliosis.
- > Greatly diminished axons in old gliotic plaques.

Peripheral Nervous System

Diseases of Peripheral Nerves

General Types of Peripheral Nerve Injury

> Axonal Neuropathies

- > Primary damage of nerve tissue targeting the Axon.
- > Wallerian degeneration:
 - > An experiment to see the morphologic hallmarks of axonal neuropathies by cutting a peripheral nerve.
 - > Distal parts begin to degenerate & disappear.
 - > Proximal parts begin to grow for repair.
 - > Regeneration is successful ONLY if the two transected ends remain closely approximated.
 - > A failure of outgrowing axons to find their distal target (as in limbs amputation) can produce a "pseudotumor" referred as Traumatic or Amputation Neuroma.
 - > a Non-neoplastic haphazard proliferation of axonal processes & associated Schwann cells that results in a painful nodule.

> Demyelinating Neuropathies

- > Primary damage targeting myelin sheath & Schwann cells w/ relatively preserved axons.
 - > Random degeneration.
- > Schwann cells begin repair attempts through formation of new myelin sheaths.
 - > The Internode segments are shorter & thinner than the original ones.
 - ↳ the myelinated segment b/w two nodes of Ranvier.
- > Electrophysiologic hallmark is slowed nerve conduction velocity due to loss of myelin.

> Neuronopathies

- > Primary damage targeting the neuronal cell body.
 - > Leading to secondary degeneration of axons.
 - > May be as a result of infections like herpes zoster & toxins like platinum compounds.
 - > Enter in the formation of Chemotherapy especially that of Colon & Rectal cancer.
 - > So, Numbness (Pins & Needles) in distal parts of limbs is a common side effect in cancer patients.
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Anatomic Patterns of Peripheral Neuropathies

> Mononeuropathies

- > Affect a single nerve & result in deficits related to distribution of affected nerve.
 - > Trauma & Infections are common causes.

> Polyneuropathies

- > Affect multiple nerves, usually in a symmetric fashion.
 - > In most cases axons are affected in a length-dependent fashion.

> Mononeuritis multiplex

- > Describes a disease process that damages individual nerves in a haphazard fashion.
 - > Vasculitis is a common cause of this pattern of injury.
 - ↳ i.e NOT symmetric.

> Polyradiculoneuropathies

- > Affect nerve roots as well as peripheral nerves, leading to diffuse symmetric symptoms.
 - > Usually concentrated in proximal & distal parts of the body.
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Specific Peripheral Neuropathies

- > Patients often complain of numbness, painful "pins & needles" sensations & weakness.
 - > Most often in distal portions of extremities.
- > Many different types of disease processes can damage peripheral nerves, including:
 - > Inflammatory diseases.
 - > Infections.
 - > Damage the nerve directly or by triggering an immune response.
 - > Metabolic changes.
 - > As in Diabetic patients as a result of Hyperglycemia or secondary to B12 defects.
 - > Toxic injury & Trauma.
 - > Paraneoplastic disease as a result of tumor products.
 - > Inherited gene defects.

> Inflammatory Neuropathies

> **Guillain-Barré Syndrome** is the prototype of this group.

> a.k.a Acute Inflammatory Demyelinating Polyneuropathy.

> Considered as counterpart of Multiple Sclerosis in Peripheral NS.

> Is an immunologically mediated demyelinating peripheral neuropathy that may lead to life-threatening respiratory paralysis.

> Annual incidence is 1/100,000 persons.

> Weakness begins from distal to proximal limbs.

> Referred as "ascending paralysis".

> Histologic features are inflammation and demyelination of spinal nerve roots and peripheral nerves (Radiculoneuropathy).

Pathogenesis

> Acute-onset immune-mediated **demyelinating** neuropathy.

> i.e Myelin destruction.

> 2/3 of cases preceded by Influenza-like illness.

> Infections w/ Campylobacter Jejuni, CMV, EBV & M.Pneumoniae as well as prior vaccination have significant epidemiologic associations.

> No infectious agent demonstrated in affected nerves.

> Experimentally there is a role of lymphocytes, macrophages & Abs.

MORPHOLOGY

> The dominant finding is inflammation of peripheral nerves.

> Manifested as perivenular & endoneurial infiltration by lymphocytes, macrophages & few plasma cells.

> Segmental demyelination affecting peripheral nerves is the most prominent lesion.

> Damage to axons is also seen, particularly when disease is severe.

> b/c myelin is the primary target.

> Inflammation is more prominent close to nerve roots "Radiculoneuropathy".

> Infectious Neuropathies

> Varicella-zoster is one of most common viral infections of Peripheral NS.

> Following chickenpox, a latent infection persists within neurons of sensory ganglia.

> If the virus is **reactivated** >> it transported along the sensory nerves to the dermatomes.

> Here it infects keratinocytes >> leading to a painful, vesicular skin rash in a distribution that follows sensory dermatomes >> referred as Shingles.

> May be due to ↓ cell mediated immunity

> Affected ganglia show neuronal death w/ abundant mononuclear infiltrates.

> Followed by degeneration of the axons.

> Metabolic Neuropathies: DM

> DM is the most common cause of peripheral neuropathy.

> 50% of Diabetic patients will develop this complication.

> M/C Pattern is ascending distal symmetric sensorimotor polyneuropathy.

Pathogenesis

- > The mechanism of diabetic neuropathy is complex.
 - > Both metabolic & secondary vascular changes contribute to damage of axons & Schwann cells.
 - > Hyperglycemia causes the nonenzymatic glycosylation of proteins, lipids & nucleic acids.
 - > Lead to activation of inflammatory signaling & release of inflammatory mediators.
 - > Result in depletion of NADPH (Antioxidant) >> damage by free radicals.
 - > The Vascular pathology may cause ischemic damage of the nerves.

MORPHOLOGY

- > The predominant finding is an axonal neuropathy.
- > Nerve biopsies show reduced numbers of axons.
- > Degenerating myelin sheaths & regenerative axonal clusters.
 - > "Amputation Neuroma"
- > Endoneurial arterioles show thickening & hyalinization.
 - > NOT specific for DM.

Diseases of the NMJ

- > The neuromuscular junction located at the interface of motor nerve axons & skeletal muscle.
 - > Here, distal ends of peripheral motor nerves branch into small processes that terminate in bulbous synaptic boutons.
 - > Presynaptic membrane is the terminal ends of the axon.
 - > Synaptic space.
 - > Postsynaptic membrane is the Sarcolemma.
 - > Upon depolarization, presynaptic nerve terminals release acetylcholine (ACh) into the synaptic cleft.
 - > The Sarcolemma contains ACh receptors.
 - > Binding of ACh to its receptors will initiate cellular events that ends by muscle contraction.
 - > Regardless of cause, patients w/ disorders that impair the function of NMJ complain of painless weakness & fatigue.
 - ↳ b/c the motor function is affected.
 - > Autoantibodies that recognize key NMJ proteins are M/C cause of disrupted neuromuscular transmission.
 - > As found in Myasthenia Gravis "grave weakness"

Myasthenia Gravis

- > Ab mediated Dz of NMJ.
- > An autoimmune Dz that is usually associated w/ AutoAbs directed against ACh receptors.
 - > or other components of NMJ.
- > It has a prevalence of 150-200/ 1 million & shows a Bimodal age distribution.
 - > i.e seen in both adults & children.

Pathogenesis

- > Autoantibodies against postsynaptic ACh receptors.
 - > These autoantibodies are Pathogenic.
 - > b/c the disease can be passively transferred to animals w/ Abs from affected individuals.
 - > & any therapeutic methods that ↓ AutoAbs levels associated w/ ↓ in symptoms.
 - > Binding of AutoAbs to ACh receptors lead to aggregation & destruction of the receptors.
 - > Followed by damage to postsynaptic membrane through complement fixation.
 - > (+) of immune system > destruction of NMJ.
 - > No further response to ACh.
 - > There is a strong association b/w this AutoAbs & Thymic abnormalities.
 - > Either Hyperplasia or Neoplasia.
 - > 10% of MG patients have a thymoma.
 - > Benign tumor of thymic epithelial cells.
 - > 30% of MG patients have thymic hyperplasia.
 - > So, thymic abnormalities promote autoimmunity against ACh receptors.
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