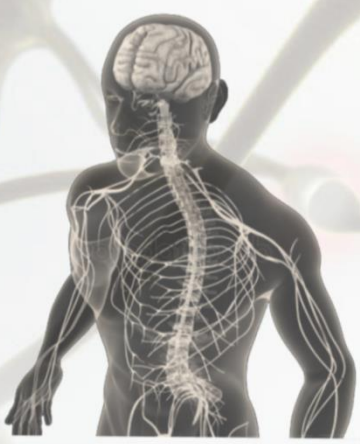
Central Nervous System

Sheet 5



Subject | Micro

Done by | Yousef Omar

Correction | ...

Doctor | Anas

***Our main subject is related to PNS.

-PNS dysfunction isn't an emergency and is part of another disease, mostly a multi systemic disease in which part of its pathology is damage of peripheral neurons.

-In general, patients with PNS dysfunction complain of:

1. Sensory disturbances: either negative symptoms like numbness, loss of sensation, Or positive symptoms like tingling, burning or both.
2. Motor disturbances like loss of muscle mass, painful cramps, or fasciculations.
3. Autonomic disturbances
4. Both (Motor , sensory, and autonomic)

-Damage in PNS happens due to vascular ,inflammatory and autoimmune reasons rather than infectious reasons. (In meningitis we said most causes are infectious and rarely non-infectious)

-Infectious causes of peripheral nervous system (PNS) disease are underrecognized but potentially treatable.

***Pathogens With Clinical Implications in the PNS:

>>>Human immunodeficiency virus, Herpes viruses, Poliovirus, Borrelia burgdorferi, Clostridium tetani, Clostridium botulinum, Mycobacterium leprae, Campylobacter jejuni.

First: HIV

-HIV is a retrovirus that is transmitted primarily by sexual contact and contaminated blood.

-Remember that HIV in CNS can be considered a cause of encephalitis, and less commonly viral meningitis. It causes CNS infection by being present in lymphocytes, which crosses BBB, so then HIV gain access to CNS and causes encephalitis.

-HIV commonly affects both the CNS and the PNS.

-**Distal symmetric polyneuropathy** (DSP) (usually paresthesias or numbness in a stocking-glove distribution) associated with HIV is the most common PNS complaint as a presenting symptom, affecting up to 30% to 50% of patients with advanced infection. This damage to PNS can also be associated with other pathologies like vasculitis and autoimmune diseases.

Note: DSP have positive and negative symptoms, sensory and motor disturbance. Distal symmetric occur in both sides effecting hands and feets. Polyneuropathy since it effect multiple nerves.

-Two distinct pathophysiologic processes are thought to contribute to the development of HIV DSP: direct neurotoxicity of the virus and its products and neurotoxicity of cART (combination antiretroviral therapy).

-HIV can also present with Inflammatory demyelinating polyneuropathy, mononeuropathy multiplex, and polyradiculopathies are present with varying degrees of immune suppression but usually **early in disease**.

Human Herpesviruses

Virus	Subfamily	Disease	Site of Latency
Herpes Simplex Virus I	α	Orofacial lesions	Sensory Nerve Ganglia
Herpes Simplex Virus II	α	Genital lesions	Sensory Nerve Ganglia
Varicella Zoster Virus	α	Chicken Pox Recurs as Shingles	Sensory Nerve Ganglia
Cytomegalovirus	β	Microcephaly/Mono	Lymphocytes
Human Herpesvirus 6	β	Roseola Infantum	CD4 T cells
Human Herpesvirus 7	β	Roseola Infantum	CD4T cells
Epstein-Barr Virus	γ	Infectious Mono	B lymphocytes, salivary
Human Herpesvirus 8	γ	Kaposi's Sarcoma	Kaposi's Sarcoma Tissue

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Second: **α-**Subfamily of Herpes simplex virus

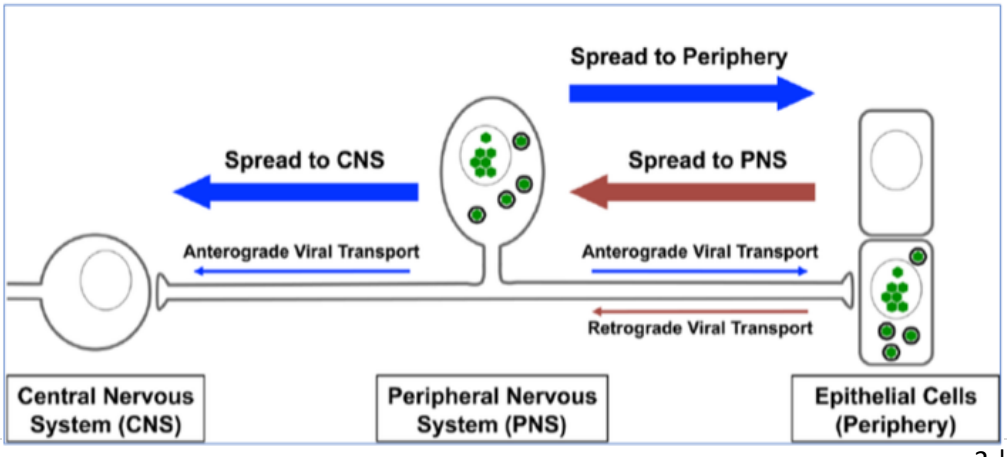
-HSV 1, 2 and VZV site of latency is in sensory nerve ganglia.

-Herpesviruses all share a common structure—relatively large, double-stranded, linear DNA genomes.

First in case of herpes viruses (HSV1 AND 2): (Both are rare)

Pathophysiology: after infecting epithelial cells in skin around mouth (HSV1) or skin in genitals (HSV2)>>> then there is viral transport, retrograde , through neurons to spend their latency in sensory nerve ganglia, then every while reactivation occur , and anterograde viral transport goes in 2 directions through neurons: (Refer to figure for better understanding)

1. To epithelial cells causing infection and rash in the skin.
2. And in case of HSV 1, anterograde viral transport might be toward the CNS casuing encephalitis. And in case of HSV 2 viral meningitis may occur.



Second in case of VZV:

-Primary infection with VZV typically occurs in childhood in form of chickenpox and is characterized by a skin rash that forms small, itchy blisters, which eventually scab over. VZV then spends its latency in sensory root ganglia, and after reactivation, it appear in the form of shingles (rash with dermatomal distribution). The most commonly reported PNS complication is **post-herpetic neuralgia(**cause severe pain), which is a dermatomal distribution pain following shingles (this complication may appear after rash disappear or it accompany the rash)

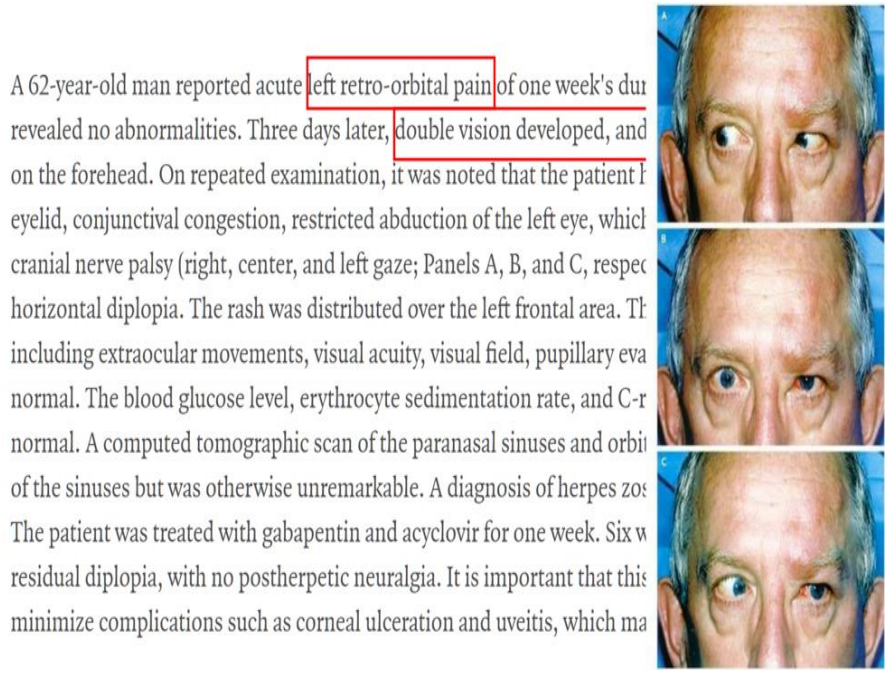
-Reactivation of VZV occurs primarily in the elderly patients, immunosuppressed, people under lots of stress and not taking good care of their health.

-Diagnosis of VZV neuropathy is primarily clinical (rash with dermatomal distribution with a history of chicken pox).

-Early treatment of VZV infection is recommended with antiviral agents such as acyclovir, valacyclovir, and famciclovir for 7 days. Also give analgesics to reduce pain in the brain.

***Case study:

>>>acute left retroorbital pain, then 3days later, he has double vision and rash appeared on the forehead which suggest that one of cranial nerves is effected. On repeated examination, it was noted that patient swelling of left upper eyelid, conjunctival congestion and restricted abduction of the left eye which is diagnostic of 6 cranial nerve palsy. Rash distributed on left frontal are. The rest of eye examination were normal. C-reactive protein levels were normal as well. So diagnosis was based on clinical presentation mainly since blood test were normal. No postherpetic neurolgia is absent (but still it can occur in case of cranial nerves).



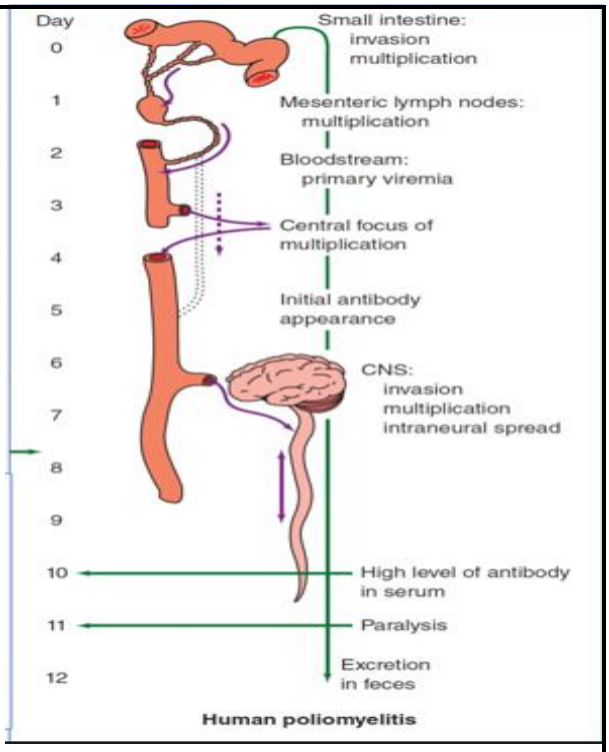
A 62-year-old man reported acute left retro-orbital pain of one week's dur
revealed no abnormalities. Three days later, double vision developed, and
on the forehead. On repeated examination, it was noted that the patient h
eyelid, conjunctival congestion, restricted abduction of the left eye, whicl
cranial nerve palsy (right, center, and left gaze; Panels A, B, and C, respec
horizontal diplopia. The rash was distributed over the left frontal area. Th
including extraocular movements, visual acuity, visual field, pupillary eva
normal. The blood glucose level, erythrocyte sedimentation rate, and C-r
normal. A computed tomographic scan of the paranasal sinuses and orbit
of the sinuses but was otherwise unremarkable. A diagnosis of herpes zos
The patient was treated with gabapentin and acyclovir for one week. Six w
residual diplopia, with no postherpetic neuralgia. It is important that this
minimize complications such as corneal ulceration and uveitis, which ma

Third: Poliovirus

-Poliovirus has been eliminated throughout the world by the regular use of vaccination (عقبال كورونا). In 2012, only 223 confirmed cases of polio were reported globally due to widespread vaccination programmes.

-Poliovirus, a member of the enterovirus family causes polio or infantile paralysis. Enterovirus are named so because primary site of replication is in the intestine and is transmitted feco-orally.

-So virus first invade and replicate in the small intestine >>> then infect mesenteric lymph nodes and replicate there>>>then it causes primary viremia in the blood>>>then it can go to other organs and seed from their to cause secondry viremia or it can directly go to CNS where it invades, multiply and start to destruct nerves causing paralysis. (Refer to figure)



-Up to 72% of all polio infections in children are asymptomatic. Fewer than 1% of all polio infections in children result in flaccid paralysis. Through vaccination, antibody will interput the virus in the blood(primary viremia), so it won't spread to CNS. So basically you get a primary infection but it will not spread to CNS.

-Diagnosis is through viral recovery from stool, or through rising antibody titer in blood.

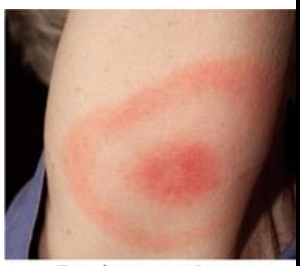
END of viral causes, the rest are bacterial casues

Fourth: Borrelia burgdorferi


Borrelia burgdorferi

-It's a spirochete,and facultative intracellular organism that is transmitted by ticks, and it can be seen by dark field microscopy since gram stain doesn't give much information.

-Borrelia cause Lyme disease, that is a multi-system infectous disease, one of them is PNS.


Erythema migrans

-Tick-borne diseases present with rash, fever and myalgia with a history of tick bite.

- In case of lyme disease caused by borrelia, it cause a specific rash called erythema migrans (as in the figure). Borrelia also causes a broad variety of peripheral nerve disorders, including single or multiple cranial neuropathies, painful radiculopathies, and diffuse polyneuropathies along with fever, myalgia and generalized pain.

-Clinical presentation(mentioned above), history(tick bite), and serology(to look for antibodies against Borrelia) are important in diagnosis. (diagnosis is challenging since it's a multisystemic disease and sometimes if patient comes to clinic late, erythema migrans would have disappeared and only comes with radiculopathies and neuropathy)

-Doxycycline is given to adults with suspected Lyme disease as first line of treatment.

***Case study:

82year-old women developed Rt-sided upper back pain that radiated to Rt arm in the setting of fever, myalgia, generalized fatigue and erythema migrans(Indicate lyme disease). She was given doxycycline for presumed lyme. Although she did have a pulsatile headache and meningismus, the back pain was much more prominent progressing to mild weakness in C6 distribution(radiculopathy), and left sided 7th cranial nerve palsy(neuropathy) which indicate involvement of PNS. She received 4 weeks ceftriaxone for presumed CNS lyme and also used pain killers.

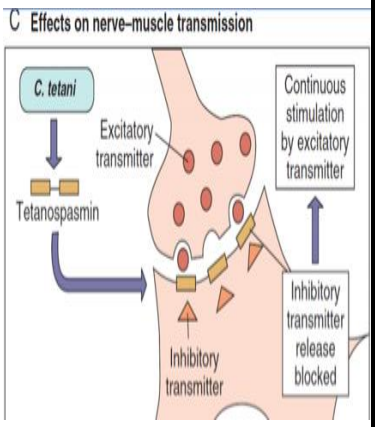
In early summer, an 82-year-old right-handed woman from Western Massachusetts developed right-sided upper back pain that radiated down the right arm in the setting of fever, myalgias, generalized fatigue, and erythema migrans just under the right clavicle. She was given a course of doxycycline for presumed Lyme but discontinued it after 3 days. Her pain worsened, and although she did have a pulsatile headache and meningismus, the back pain was much more prominent, progressing to mild weakness in a C6 distribution. She also developed a left-sided cranial nerve VII palsy. She received 4 weeks of IV ceftriaxone for presumed CNS Lyme. Her pain regimen included fentanyl transdermal patch 25

Fifth: Clostridium tetani

-Clostridium are gram positive spore forming ,anaerobic, bacteria. Each type of clostridium secrete a toxin: **1.** Clostridium tetani cause spastic paralysis **2.** Clostridium botulinum which cause Flaccid paralysis.

First in the case of clostridium tetani:

-C. tetani produces tetanospasmin, which inactivates proteins that regulate release of the inhibitory neurotransmitters glycine and gamma-aminobutyric acid (GABA)>>> This leads to unregulated excitatory synaptic activity in the motor neurons, resulting in spastic paralysis.

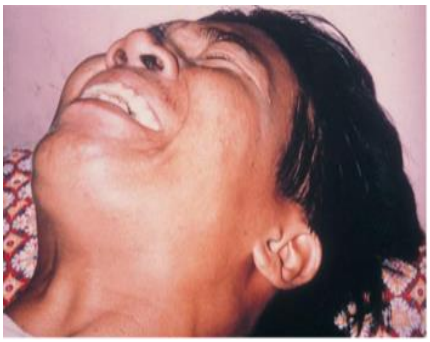


-Disease is relatively rare because of the high incidence of vaccine-induced immunity(toxoid vaccine).

-So first the patient gets a damage that cause a cut/wound, then the toxin that is produced locally goes into circulation and then it starts to act on nerves causing decrease in release of inhibitory transmitter like GABA leading to continuous stimulation and spasm.

-spasm of the masseter muscles (trismus or lockjaw) is the presenting sign in most patients, which leads to the characteristic sardonic smile that results from the sustained contraction of the facial muscles. (Refer to figure)

-Sometimes it's a more generalized spasm.



unregulated excitatory synaptic activity in the motor neurons, resulting in **spastic paralysis. Generalized tetanus** is the most common form.

***How to treat and diagnose clostridium tetani?

-Diagnosis is based on physical examination , immunization history and clinical presentation, while less emphasis is placed on laboratory testing.

-In both spastic and flaccid paralysis, you should pay attention to respiratory muscles. That's why you may admit the patient to ICU and Some patients may even require mechanical ventilation. (Supportive therapy)

-Other than supportive therapy, try to neutralize the toxin with antibodies in the form of passive immunity>>> so give tetanus immunoglobulin (Most important) and antibiotics (penicillin G to treat clostridium tetani). Also It is important to note that antimicrobial therapy plays a relatively minor role in the management of tetanus and of primary importance is **wound debridement** (where bacteria is replicating and secreting toxin) and toxin mitigation.

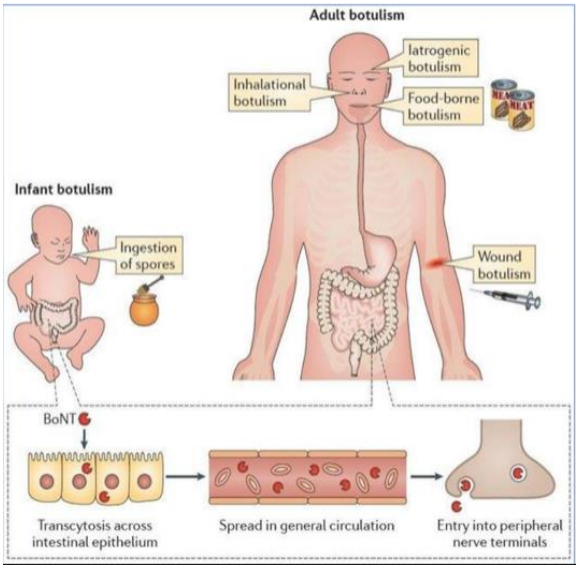
Second in the case clostridium botulinum:

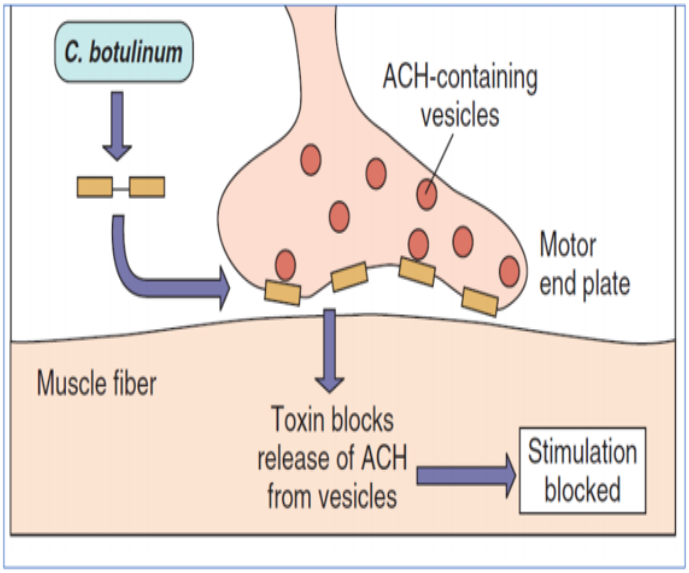
-C. botulinum is a spore-forming, anaerobic, Gram positive rod.

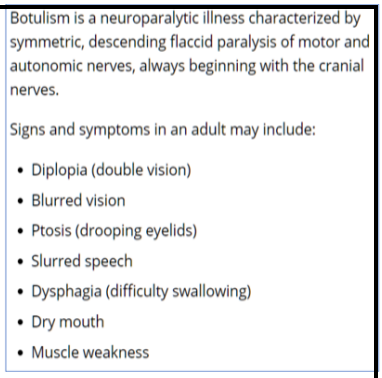
-Clostrida and bacilli spp. are ubiquitous pathogen, so if a wound gets dirty due to exposure to soil, then expect wound infection by some of these ubiquitous organism. But the common way by which we get infected by C. botulinum is through ingestion of home-canned food.

-Spores of bacteria have developed into primitive state, and started forming toxin inside closed canned food, so you ingest food contaminated with toxin, which then is absorbed and goes into blood, then heads to nerve terminals .The botulinum neurotoxin remains at the neuromuscular junction, The botulinum endopeptidase then inactivates the proteins that regulate release of acetylcholine, blocking neurotransmission at peripheral cholinergic synapses leading to flaccid paralysis.

-C. botulinum toxin is composed of A-B unit, B-binding subunit binds to the surface and A subunit goes in to inactivate proteins that regulate release of Ach.







-The typical presentation of botulism is descending paralysis that almost always starts from cranial nerves, so one of the earliest signs in adults is diplopia, blurred vision, ptosis and slurred speech, then later on it starts to progress more down leading to weakness and paralysis of hands, feets,..etc.

***How to diagnose and treat C. Botulinum?

-Initial diagnosis is based on clinical symptoms. Laboratory confirmation is done by demonstrating the presence of botulinum toxin in serum, stool, or food, or by culturing C. botulinum from stool, or a wound.

-It's treated like C. tetani, by giving supportive treatment. Also make sure that respiratory Ms are working properly, otherwise using mechanical ventilation because death is most commonly attributed to respiratory paralysis . Also neutralize the toxin by use of antibodies.

Note: Supportive care and the use of antitoxin have been effective in the treatment of botulism from food-borne, intestinal, and wound exposure. However, the effectiveness of antitoxin in the treatment of inhaled C. botulinum has not been proven.

***In case of infants, C. botulism cause **infant botulism**, because it seems that honey contains spores of C. botulism. So when ingested those spores pass through GIT, and because they don't have a mature microbiota, these spores turn into vegetative state and produce the toxin. This problem isn't found in adult since spores won't find any place to flourish in intestine. So CDC recommends that children under 12months of age are not allowed to eat honey.

END of pathogens responsible for clinical applications in PNS

***Now let's start with Gut brain axis:

-In clinical practice, evidence of microbiota-GBA interactions comes from the association of dysbiosis (abnormal microbiota) **with** central nervous disorders (i.e. autism, anxiety-depressive behaviors) and functional gastrointestinal disorders (heritable bowel syndromes).

-Most of the data have been acquired using technical strategies consisting in germ-free animal models, probiotics, antibiotics, and infection studies.

-So studies were intiated to understand the effect of microbiota on CNS by using germ-free animal models. So they brought a mice with no microbes and started to see the effect in mice after applying microbes, also studies on the behavior of the mice to microbe in absence of gut microbiota.

-it was found that when some mices were given certain strains of lactobacilli, autism symptoms in these mices would decline.

-So its seems that manipulating the gut microbiota, it can effect the CNS functions of cognitive functions/mood/…

Symbiotic microbes have been shown to regulate nutrition and metabolism and are critical for the development and function of the immune system. More recently, studies have suggested that gut bacteria can impact neurological outcomes--altering behaviour and

potentially affecting the onset and/or severity of nervous system disorders.

**How this occur?

***First in case of gut microbiota control of brain: (Refer to figure)

- It seems that diversity of bacteria and species and their numbers are important, so through its chemical metabolites like serotonin and short chain fatty acid can effect the brain.
- Also they play a role in immune signaling by soluble IgA found in the mucos and also binds to microbiota and signal immune cells.
- They effect barrier integrity which is sensed by CNS.
- Barrier integrity, immune signaling and metabolites can work directly as neurotransmitters.
- Also they metabolize neurotransmitter controlling their activity which influence the brain.
- Modulation of enteric sensory afferent and vagus nerve.

From gut microbiota to brain:
Production, expression and turnover of neurotrasmitters (i.e. serotonin, GABA) and neurotrophic factor (BDNF)
Protection of intestinal barrier and tight junction integrity
Modulation of enteric sensory afferents
Bacterial metabolites
Mucosal immune regulation

***Second in case of brain control to gut microbiota: as in the figure below:

From brain to gut microbiota:
Alteration in mucus and biofilm production
Alteration in motility
Alteration of intestinal permeability
Alteration in immune function

***These interactions helped us understand some diseases like irritable bowel syndrome (IBS), which is considered a functional gastrointestinal disorder, which is now considered a microbiome-GBA disorder.