CNS
MICROBIOLOGY

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Microbiology of the PNS

QUICK INTRO

- **CNS** infections are more **common** and more **severe** than PNS infections. For example, meningitis, encephalitis (inflammation of the brain), and space-occupying lesion of the brain are considered medical emergencies.
- In **PNS diseases**, the cause of damage is **rarely** due to **infections**. As a result, infectious causes of the PNS are **under-recognized but potentially treatable**.
- **Vascular** (like ischemia) and primary **inflammatory** (like vasculitis) or **autoimmune** causes are **more common** causes of PNS diseases.

Category	Examples
Traumatic	Incision, compression, stretching
Metabolic	Diabetes, renal failure, hypothyroidism, amyloid
Malignancy	Especially small cell carcinoma of the lung
Drugs	Isoniazid, phenytoin, nitrofurantoin
Toxins	Lead, alcohol
Infections	Leprosy (the commonest cause worldwide), Lyme disease, HIV
Inflammatory	Guillain-Barré, sarcoid
Vascular	Prolonged ischaemia, polyarteritis nodosa, rheumatoid disease
Genetic	Charcot-Marie-Tooth disease, porphyria
Vitamin deficiencies	B1, B6, B12, nicotinic acid

- The pathogens with clinical implications in the PNS are:

1) Human immunodeficiency virus
2) Herpes viruses
3) Poliovirus
4) Borrelia burgdorferi
5) Clostridium tetani
6) Clostridium botulinum
7) Mycobacterium leprae
8) Campylobacter jejuni

- Some of these pathogens result in a huge damage to the PNS, while others might contribute a little damage to the PNS.
- Depending on which pathogen is present, we will have different signs and symptoms. Also, the signs and symptoms might differ throughout the course of the disease, for example, an HIV patient will have different neuropathies in early vs. late stages.
- There is more than one presentation for PNS infections; patients with PNS dysfunction complain of:

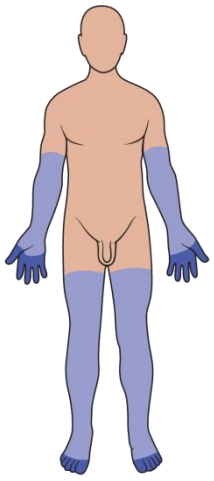
- ✓ **Sensory Disturbance:** These presentations could be **negative** symptoms, such as numbness and loss of sensation, OR **positive** symptoms, such as tingling, burning, or both(a general increase in pain sensation).
- ✓ **Motor Weakness:**e.g. flaccidity, spasms, paralysis, loss of muscle mass, painful cramps or fasciculation.
- ✓ **Autonomic Disturbance:**e.g. loss of bladder function, gut motility disturbances.
- ✓ **Combination of All (sensory, motor, and autonomic) in several different distributions.**

- The **history** of the patient AND the **distribution of the weakness** or disturbance are **VERY IMPORTANT** in the diagnosis of the pathogen. (as you can see in the picture below)
- Now, let's discuss each pathogen on its own ;)

VIRAL PATHOGENS

1. Human immunodeficiency virus (HIV)

- HIV is a **retrovirus** that is transmitted primarily by **sexual contact** and **contaminated blood**.
- HIV commonly affects both the **CNS** and the **PNS**. The virus first reaches the PNS then it enters the CNS through the spinal cord.
- HIV could be presented in a different way at different stages:
  - ✓ **Distal symmetric polyneuropathy (DSP)** is usually paresthesia or numbness in a **stocking-glove distribution**, associated with HIV. It's the **most common PNS complaint**, affecting up to 30% to 50% of patients **with advanced infection (at a late stage)**.

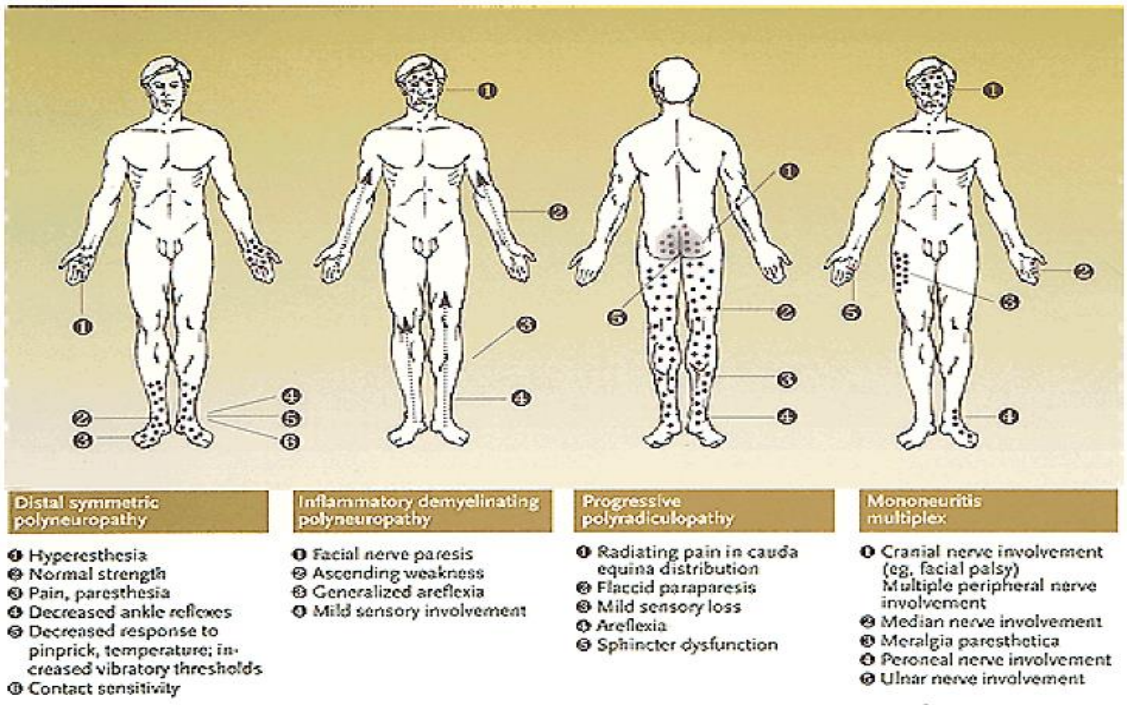


> A case suggested by Dr.Anas:
>
> A patient that has been living with HIV for a long period of time (late stage) and has been taking medications ever since, presents now with numbness or tingling in the hands and feet (stocking-glove pattern) which indicates that the patient has distal symmetric polyneuropathy.

  - ✓ **Inflammatory demyelinating polyneuropathy (IDP)** (EXTRA : is a rare neurological disorder in which there is **inflammation** of nerve roots and peripheral nerves and **destruction** of the fatty protective covering (**myelin sheath**) of the nerve fibers.) where the patient will experience **weakness in an ascending pattern**.

- ✓ **<u>Progressive polyradiculopathies</u>** (EXTRA: **radiculopathy** refers to damage to a spinal nerve root sufficient to produce neurologic symptoms and signs such as pain, weakness, and sensory loss)
- ✓ **<u>Mononeuritis complex</u>** where a single region innervated by a single neuron is damaged.
- ✓ Inflammatory demyelinating polyneuropathy, mononeuritis multiplex, and polyradiculopathies are present with varying degrees of immune suppression but usually **early in the disease**.

- Manifestations of different neuropathies that occur in HIV can be either due to **<u>direct neurotoxicity of the virus</u>** and its viral products OR due to **<u>neurotoxicity of the medications</u>** used like cART (combination antiretroviral therapy).
- If the medication is neurotoxic, then the dose should be reduced.



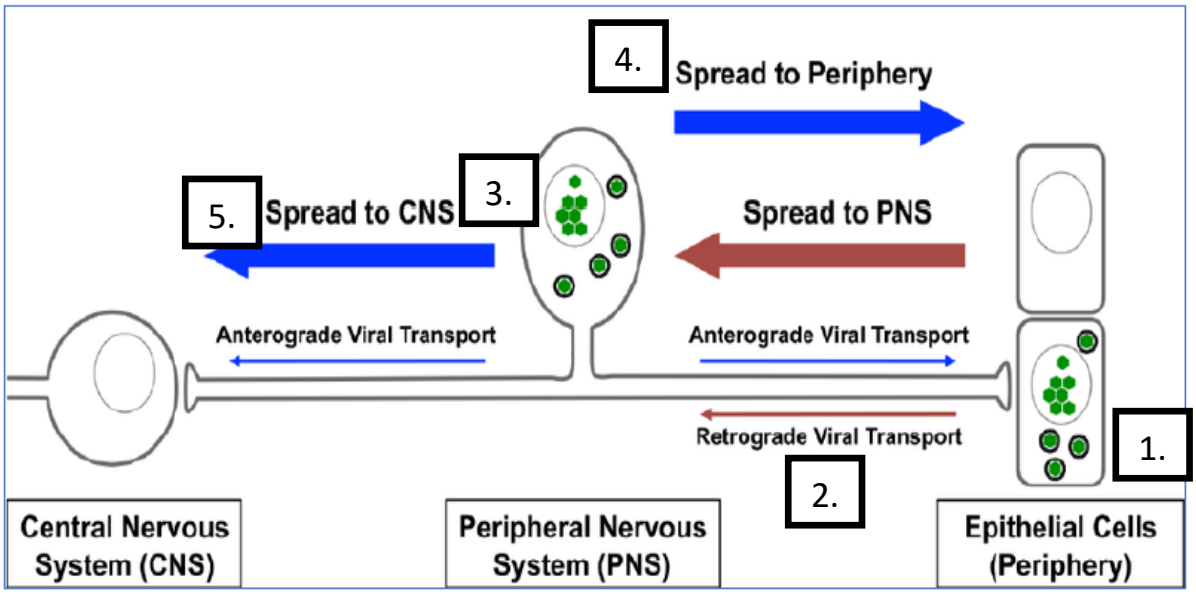
2. <u>HERPES VIRUS</u>

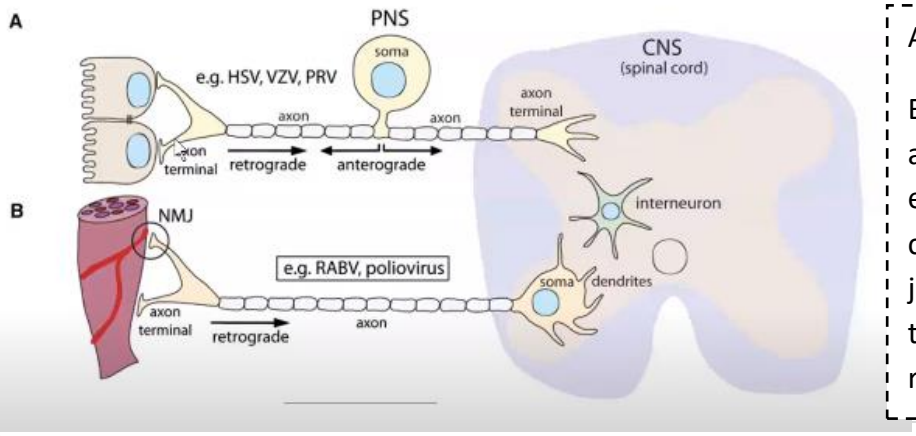
- Herpes viruses all share a common structure—relatively **large**, **double-stranded, linear** DNA genomes.
- This group of viruses infect the PNS and have a **<u>latent, recurring infections</u>.**

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

1. In their hosts, alpha herpes virus infections typically **initiate** at peripheral sites, such as **mucosal epithelia**, then the **viral particles get internalized** into the neuron
2. It then travels to the **dorsal root ganglia** along the microtubules in the axon in the **retrograde** direction towards the cell bodies, to survive there for a **lifetime, in a latent form**.
3. A latent infection is when they stay **dormant** in the dorsal root ganglia for your **whole lifetime** (their DNA is in the dorsal root ganglion, but their viral particles cannot be detected). Every now and then, they are reactivated and cause damage.
4. For an unknown reason (could be due to **stress or immune system**), the body loses immune control over the virus (**immune dysregulation**) where the **virus is reactivated** (new viral products are assembled) and travels in the **anterograde** direction, **back to the epithelial cells** to express some clinical implications. For example, HSV causes orofacial rash (stress during exams)
5. In some cases, infection may also spread trans-neuronally, from the **PNS to the CNS**. It enters the spinal cord then the brain, causing lethal encephalitis but this is **rare**.Reactivation at the epithelial cells is way more common.





A = same as previous picture.

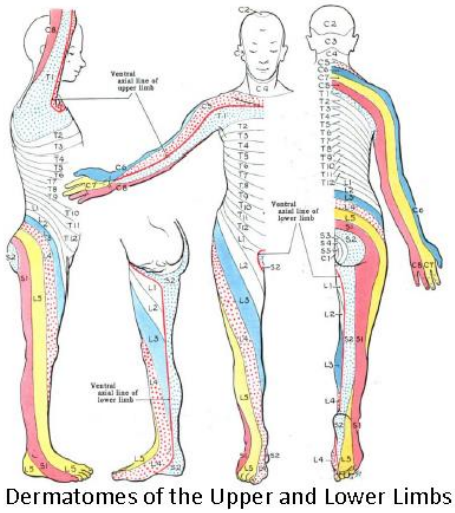
B = Other viruses like RABV and polioviruscauses encephalitis. These viruses come from neuromuscular junctions, then travel along the axonal microtubules, reaching the CNS.

- One of the members of the alpha herpes virus subfamily is the **Varicella Zoster virus.**
- **Primary** infection with VZV typically occurs in **childhood** and is characterized by a skin rash that forms small, itchy blisters, known as **chickenpox** which eventually scab over.
- **Reactivation** of VZV occurs primarily in the **elderly** patients and **immunosuppressed**, in the form of **shingles**.
- The **shingles** appear in a **dermatomal distribution;** it infects the dorsal root ganglia of the sensory neuron innervating that dermatome. For example, in the picture below, the shingles appeared in the dermatome supplied by the T1 spinal nerve, in other words, the VZV has infected the dorsal root ganglia of T1.
- When shingles disappear, **post-herpetic neuralgia** occurs (VERY IMPORTANT), which is **dermatomal distributed pain** following shingles.
- The **most commonly reported PNS complication** is post-herpetic neuralgia.
- **Diagnosis** of VZV neuropathy is primarily **clinical.**
- When you notice these shingles, you should try **early treatment** of VZV infection, which is recommended with antiviral agents such as **acyclovir**, valacyclovir, and famciclovir for **7 days**, to reduce the chance of post-herpetic neuralgia.(VERY IMPORTANT)
- Early diagnosis and early treatment can help to reduce the chance of post-herpetic neuralgia.
- REMEMBER!! infectious diseases of the PNS are rare but potentially curable. If treated, you can reduce the damage to PNS.
- Can also be associated with nerves related to vision (cranial nerves).

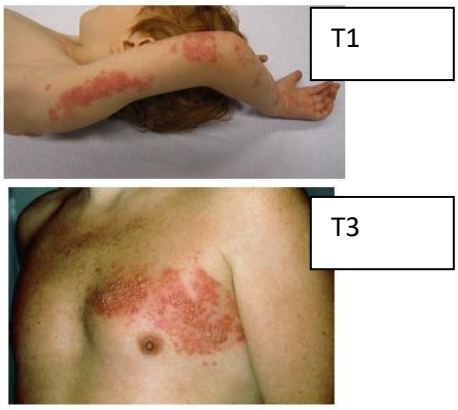
A case suggested by Dr.Anas:

a 75-year-old patient had **rash (shingles)** on his trunk and arm, then **disappeared** leaving that area of skin with sensation of **pain(post-herpetic neuralgia).**

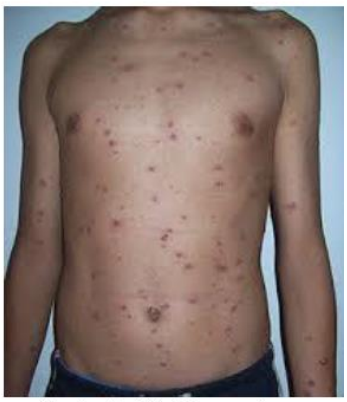
SUMMARY = VZV infects --> chickenpox --> goes away and becomes dormant --> reactivation --> shingles --> goes away --> post-herpetic neuralgia



Dermatomes of the Upper and Lower Limbs



shingles



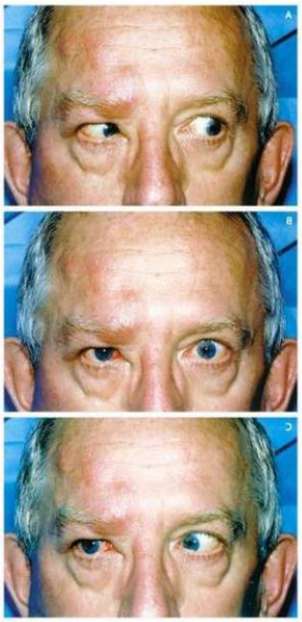
Varicella (Chickenpox)

UNCOMMON CASE:

A 62-year-old man reported acute left retro-orbital pain of one week's duration. Physical examination revealed no abnormalities. Three days later, double vision developed, and the next day a rash appeared on the forehead. On repeated examination, it was noted that the patient had swelling of the left upper eyelid, conjunctival congestion, restricted abduction of the left eye, which is diagnostic of a left sixth cranial nerve palsy (right, center, and left gaze; Panels A, B, and C, respectively), and binocular horizontal diplopia. The rash was distributed over the left frontal area. The rest of the eye examination, including extraocular movements, visual acuity, visual field, pupillary evaluation, and funduscopy, was normal. The blood glucose level, erythrocyte sedimentation rate, and C-reactive protein level were normal. A computed tomographic scan of the paranasal sinuses and orbits showed thickened mucosa of the sinuses but was otherwise unremarkable. A diagnosis of herpes zoster ophthalmicus was made. The patient was treated with gabapentin and acyclovir for one week. Six weeks later, he had minimal residual diplopia, with no postherpetic neuralgia. It is important that this diagnosis be made early, to minimize complications such as corneal ulceration and uveitis, which may threaten vision.

Notes about this case:

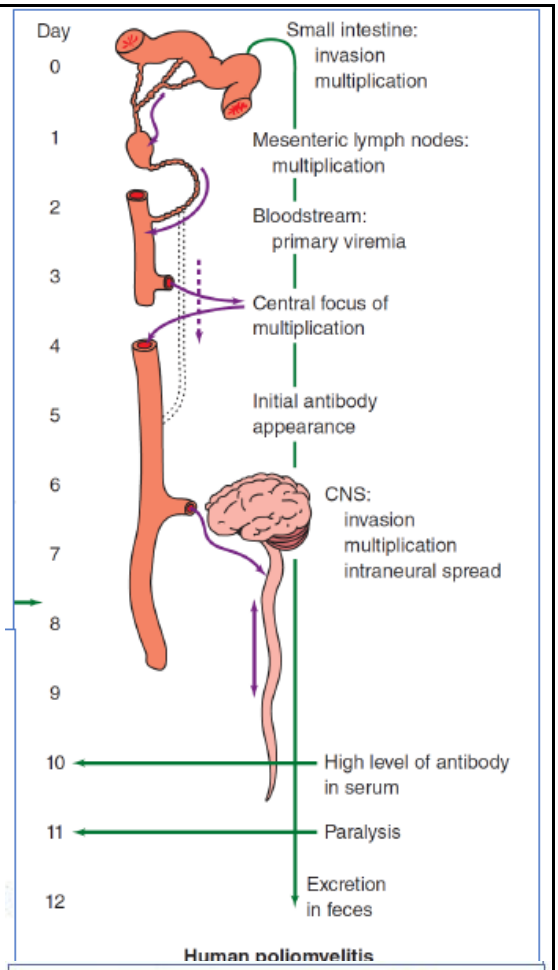
- The damage to the cranial nerves appeared earlier than the rash.
- The cranial nerve infected is the Ophthalmic nerve.
- ACYCLOVIR was given for the infection and GABAPENTIN was given to reduce the pain.
- Why "no post-herpetic neuralgia"? because of EARLY diagnosis and EARLY treatment.

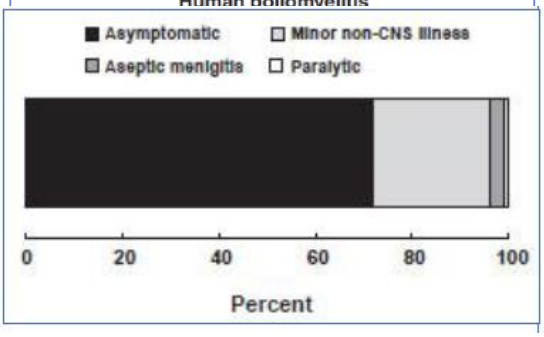


3. POLIOVIRUS

- Poliovirus, a member of the enterovirus family, causes polio or infantile paralysis.
- Poliovirus has become a **rare cause of flaccid paralysis**, due to widespread vaccination programs, where only 223 confirmed cases of polio were reported globally in 2012.
- Since it is an enterovirus, the mode of **transmission is fecal-oral** route.
- After ingestion, the virus starts multiplying in the small intestine. Then it goes to the lymph nodes, or directly into the bloodstream.

- When it reaches the bloodstream, there are 2 scenarios.
  - ⇨ Scenario 1: If the person was **vaccinated against polio**, he/she will have enough antibodies in the blood to prevent viremia and the virus **won't reach the CNS**.
  - ⇨ Scenario 2:If **NO vaccine** was taken, the antibodies will **START** to form when the virus reaches the blood, and in the meantime, the virus **will reach the spinal cord (CNS)**. Upon its arrival to the CNS, the virus will damage the neurons innervating the muscles, leading to **flaccid paralysis**.Fewer than 1% of all polio infections in children result in flaccid paralysis.





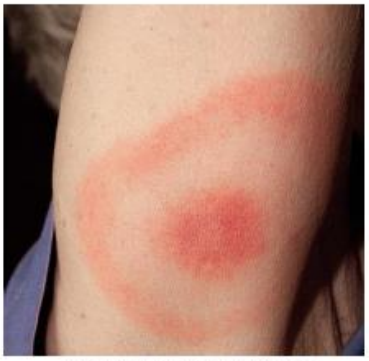
- Even if the person becomes infected, up to 72% of all polio infections in children are **asymptomatic** but if symptoms appear, it can be **very severe** like **meningitis** and **flaccid paralysis**. That's why the vaccination programs are important ;)
- There are 2 polio vaccines: (1) inactivated polio (killed) vaccine AND (2) oral polio (attenuated) vaccine.
- The oral polio vaccine is <u>not given to immunocompromised</u> individuals because in rare cases, the weakened virus can mutate and become infective again and cause paralysis.
- **Diagnosis** is through viral recovery from **stool**, or through rising **antibody titer** in blood.

BACTERIAL PATHOGENS

1. <u>Borrelia burgdorferi</u>

- **Lyme disease**, a multisystem infectious disease caused by the **tick-bornespirochete *Borrelia burgdorferi***. It causes a broad variety of peripheral nerve disorders, including single or multiple **<u>cranial neuropathies</u>**, painful **<u>radiculopathies</u>**, and diffuse polyneuropathies.

- The microscope used is **dark-field microscopy** because these spirochetes can be very thin that they cannot be visualized with gram stain and normal bright field microscopy.
- **Diagnosis:** we also use serology to test for antibodies
- **Clinical presentation, history, and serology** are important in diagnosis.
- **Doxycycline** is given to adults with suspected Lyme disease.



Erythema migrans

Borrelia burgdorferi

A case suggested by Dr.Anas:

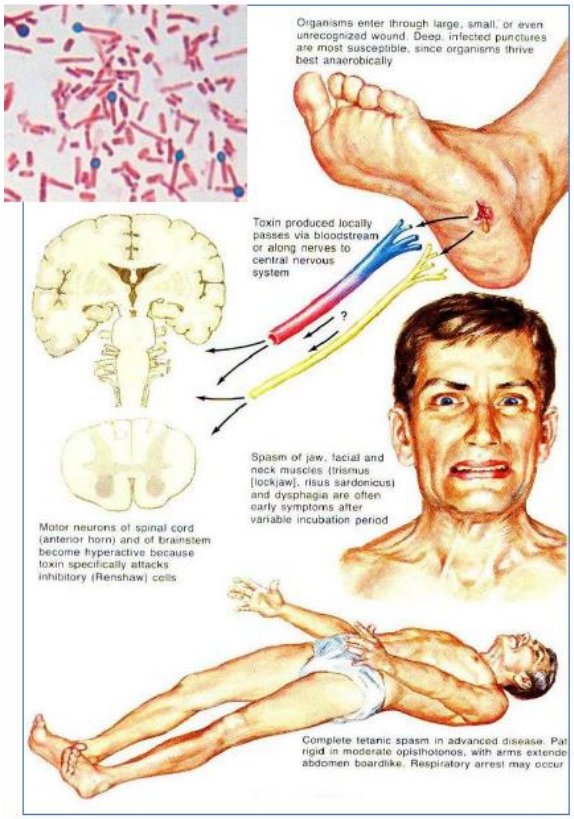
A patient went on a hiking trip. The day after, the patient presents with painful polyradiculopathy, associated with fever, myalgias, generalized fatigue and a rash, what do we expect?

Answer= tick-borne diseases in general, most probably Lyme disease. The rash that is present at the site of the tick bite is called **erythema migrans** which appears as a target sign. Plus, the **painful radiculopathy** is a strong indicator of Lyme disease. Also, the history is very important in this case (hiking trip).

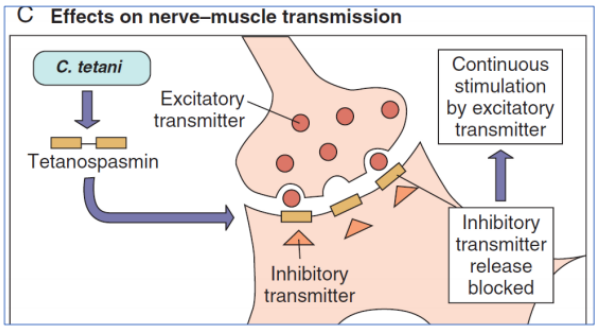
In early summer, an 82-year-old right-handed woman from Western Massachusetts developed right-sided upper back pain that radiated down the right arm in the setting of fever, myalgias, generalized fatigue, and erythema migrans just under the right clavicle. She was given a course of doxycycline for presumed 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

REMEMBER!! Both **cranial neuropathies** and **painful radiculopathies** are strong indicators of Lyme Disease.

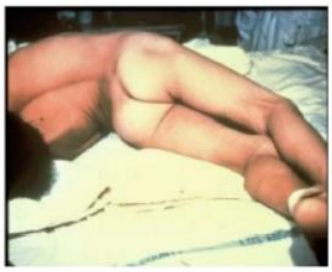
2. Clostridium tetani



- *C. tetani* is a **spore-forming**, anaerobic, **Gram positive** rod that causes **tetanus**.
- *C. tetani* produces a toxin called **tetanospasmin**.
- When there is a **cut** in the hands or legs, AND the person is **unvaccinated**, then the bacteria will start to propagate at the site of injury, producing a **toxin** in the blood that will go to the **PNS**, especially the **motor neurons** OR **directly** affecting the neurons in the vicinity.
- This disease is relatively **rare** because of the high incidence of **vaccine-induced immunity**.
- The vaccine is a **toxoid vaccine,** which is a vaccine that works best with toxin-mediated bacteria.
- Tetanospasmin **inactivates**/inhibits proteins that regulate release of the **inhibitory neurotransmitters;** glycine and gamma-aminobutyric acid (GABA). This leads to **continuous stimulation**, and unregulated excitatory synaptic activity in the motor neurons, resulting in **spastic paralysis**.

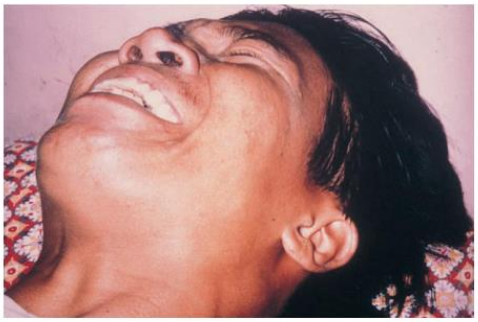


- The **spastic paralysis** can be generalized OR specific to certain muscles like facial muscles **(sardonic smile)**.



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

- **Diagnosis** of tetanus is usually based on physical exam, immunization history, and clinical presentation, while less emphasis is placed on laboratory testing.
- **Treatment** for unvaccinated patients is **passive immunity,** where antibodies are given.

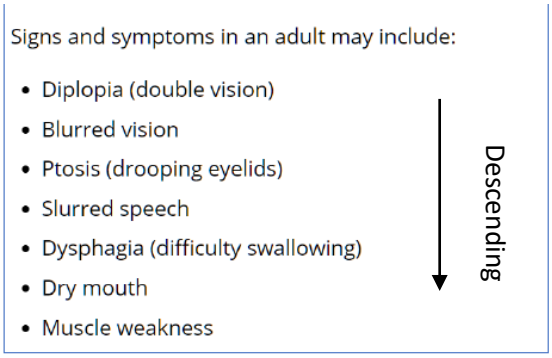


Involvement of the masseter muscles (trismus or **lockjaw**) is the presenting sign in most patients. The characteristic **sardonic smile** that results from the sustained contraction of the facial muscles.

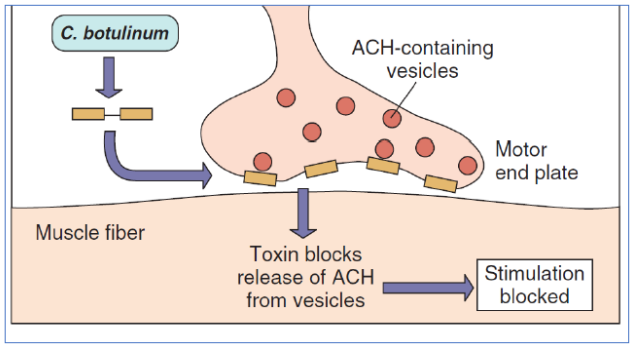
- Per current recommendations, **human tetanus immunoglobulin should be given as soon as tetanus is suspected,**at a dose of 3000 to 6000 units. The immunoglobulin will **attach to the toxin and neutralize it**.
- Antimicrobial therapy is typically metronidazole as the preferred treatment for tetanus with penicillin G as an option for second-line therapy with a treatment duration of 1 week to 10 days.
- It is important to note that **antimicrobial therapy (least important)** plays a relatively minor role in the management of tetanus compared to the **PRIMARY IMPORTANCE of wound debridement (to get rid of focus and bacteria) and toxin mitigation (passive immunity)**
- In other words, remove the focus where the bacteria have propagated and give IVIgs to the patient.
- **Admission to the ICU is highly recommended**. The **respiratory muscles could undergo spastic paralysis** so some patients may even require **mechanical ventilation**.
- Unnecessary procedures and manipulations should be avoided. The patient should be in a quiet room with low traffic.

3. Clostridium botulinum

- *C. botulinum* is a **spore-forming**, anaerobic, **Gram positive** rod that causes **botulism**.
- Botulism is a neuroparalytic illness characterized by symmetric, **DESCENDING flaccid paralysis** of motor and autonomic nerves, **always beginning** with the **cranial nerves**.

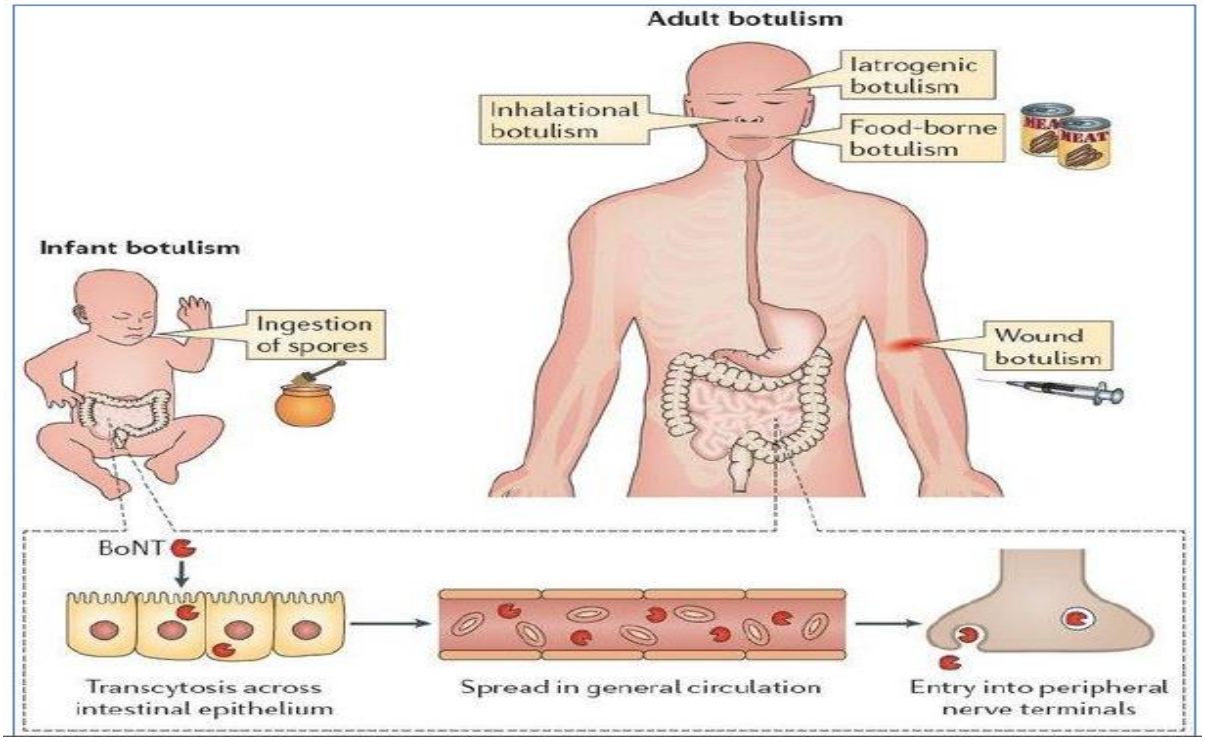


- Patients with **food-borne botulism** (most are associated with consumption of home-canned foods) typically become weak and dizzy 1 to 3 days after consuming the contaminated food. **Bilateral descending weakness** of the peripheral muscles develops in patients with **progressive disease (flaccid paralysis)**, and death is most commonly attributed to **respiratory paralysis**, as it could cause damage to the respiratory muscles where the patient might need mechanical ventilation.
- The **botulinum neurotoxin** remains at the neuromuscular junction, and the botulinum endopeptidase then **inactivates** the proteins that regulate the



release of acetylcholine, and blocks neurotransmission at peripheral cholinergic synapses, leading to **decreased muscle stimulation.** The resulting clinical presentation of botulism is **flaccid paralysis**.

- Initial **diagnosis** is based on **clinical symptoms** and **history** (important).
- 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.
- **Treatment: Supportive care** and the **use of antitoxin** have been effective in the treatment of botulism from **food-borne**, intestinal, and **wound exposure** (Remember! *C.botulinum* is a ubiquitous organism(found everywhere) so it can enter a wound from soil or dirt etc.). However, the **effectiveness** of antitoxin in the treatment of **inhaled** C. botulinum (transmission is **rare** through inhalation) has not been proven.
- **Infant botulism**: Associated/**more common** with consumption of foods (e.g., **honey**, infant milk powder) contaminated with **botulinum spores,** and ingestion of spore-contaminated soil and dust (the adult won't be infected with infant botulism). In contrast with foodborne botulism, this disease is caused by neurotoxin produced **in vivo** by *C. botulinum* colonizing the GI tracts of infants.
- In other words, **food-borne botulism** occurs after **toxin ingestion**, while **infant botulism** occurs after consuming **botulinum spores**.
- How do these spores reach the honey? Still unknown but as you know spores are resistant to any disinfection.
- Why adults are not infected by infant botulism? it seems that **adults'** gut microbiota **inhibits** the multiplication/**survival of the spores** or inhibits the change of the spore-form to the vegetative-form that can multiply. The yet to be fully established microbiota in infants is **susceptible** to *C.botulinum* spores. The spores change into a vegetative form, then **multiplies** to reach the nerve endings through the blood, resulting in **flaccid paralysis**.
- This disease is potentially curable, so early management with supportive care and the use of antitoxin is vital to prevent respiratory paralysis.
- Note: Both infections with *C.tetani* and *C.botulism* require supportive care and the use of antitoxin.
- **A possible case** (mentioned by Dr.Anas)= ingested food + descending weakness starting from the cranial nerves.



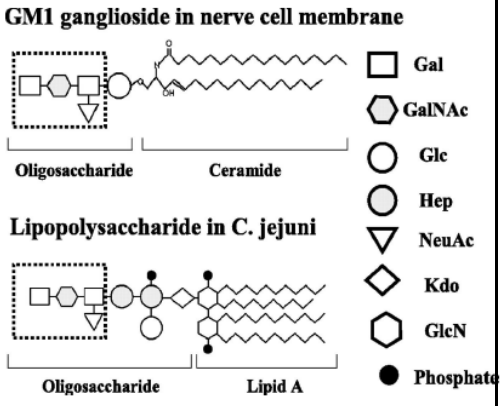
4. Campylobacter jejuni

- Infection with C. jejuni is a common cause of **bacterial gastroenteritis**.
- It causes diarrhea in general, specifically **bloody diarrhea**.
- Campylobacter infections are **zoonotic** (mainly **Contaminated poultry**/meat)
- In some cases, the immune system start forming **antibodies** against the Lipopolysaccharide/**LPS** (cell wall) or oligosaccharide in *C.jejuni*. However, the antibody structure is **similar to gangliosides'**, found in the cell membrane of **neurons**.
- **Molecular mimicry** between sialylated **lipopolysaccharide** structures on the cell envelope of these bacteria and **ganglioside** epitopes on the human nerves that generates **cross-reactive immune response** (the formed antibodies will attack the gangliosides and this causes inflammation in the neurons), resulting in **an autoimmune-driven nerve damage**, called **Guillain-Barré Syndrome (GBS)**.

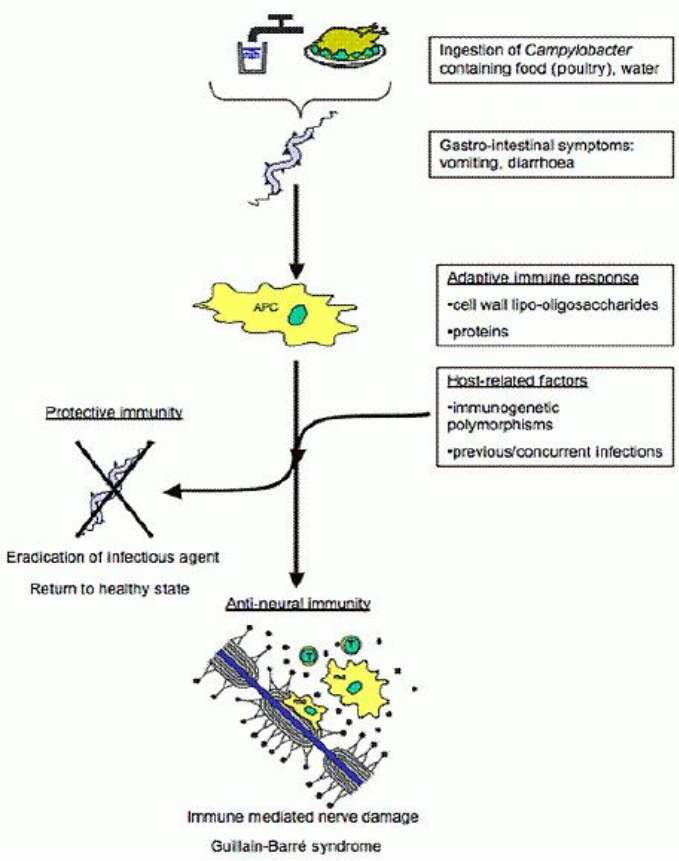
Microbiological finding	No. (%)	95% CI, %
Stool pathogen isolated[a]	168 (30.6)	27–35
Shigella species	84 (15.3)	12–19
Salmonella species	32 (5.8)	4–8
Campylobacter species	34 (6.2)	4–8
STEC	14 (2.6)[b]	1–4
Other enteropathogens[c]	9 (1.6)	1–3

NOTE. STEC, Shiga toxin–producing *Escherichia coli*.
[a] Three patients' stool specimens yielded 2 enteropathogens; each *Shigella* plus 1 each *Plesiomonas* or *Salmonella* species or *E. coli* O111.
[b] Includes 6 confirmed and 8 possible STEC cases.
[c] Vibrio (4), *Yersinia* (4), *Plesiomonas* (1) species.

Microbiological findings among US emergency department patients presenting with 549 episodes of bloody diarrhea at 11 *EMERG*Ency ID NET sites.



- C. jejuni is now considered as a **major triggering agent** of Guillain-Barré syndrome (GBS).
- **Guillain-Barré syndrome** (GBS) is an **immune-mediated demyelinating polyneuropathy** of PNS characterized by acute or subacute symmetrical **ASCENDING motor weakness**, areflexia (loss of reflexes), and mild-to-moderate (some) sensory abnormalities
- These symptoms PLUS diarrhea/bloody diarrhea in the past 2 weeks, then the patient has **GBS secondary to infection of C.jejuni**.
- **Treatment of GBS** is required for managing severely paralyzed patients, who need **intensive care** and **ventilator support** and to minimize the nerve damage. Treatments such as plasma exchange and intravenous immunoglobulins (IVIg) are indicated for patients who are unable to walk independently, while corticosteroids are largely ineffective in GBS.
- **A possible treatment is Plasmapheresis or plasma exchange:** after infection, there will be antibodies against gangliosides, present in the blood. These antibodies can be removed by getting rid of the plasma and replacing it with **new plasma** OR give **IVIg**. But why IVIg? Not clear yet but most probably the reason is that some antibodies have an inhibitory effect on the immune system where they bind to receptors and dampen their immune response (**feedback inhibition**), so they will decrease the production of new Igs against the gangliosides and this will minimize the nerve damage.
- **if only *C.jejuni* with diarrheas present,** then the treatment is**: Oral rehydration therapy**, because the infection is self-limiting , leaving not much room for antimicrobial therapy, unless the bloody diarrhea is very severe and invasive.
- How to prevent GBS or reduce the chance of its occurrence after infection with *C.jejuni* ? We don't know ;) so the best solution is **prophylaxis** (to not get *C.jejuni*). For instance, eat well-prepared food.
- A presumptive identification of isolates is based on growth under selective conditions (microaerophilic), and typical microscopic morphology (curved, gramnegative rods).



MYCOBACTERIAL PATHOGENS

1. Mycobacterium leprae

- **Leprosy** جذام(Hansen's disease) is one of the most common causes of non-traumatic peripheral neuropathy in the developing world.
- It was feared by many people because of **disfigurement** (تشوه)
- The disease mainly affects the **skin**/epithelia, the **peripheral nerves**, **mucosal** surfaces of the upper respiratory tract and the eyes.
- The causative agent, **Mycobacterium leprae**, has a predilection **for Schwann cells** (a type of glial cells that form myelin in PNS), where the organism multiplies, unimpeded by organism-specific host immunity, resulting in **destruction of myelin**, secondary inflammatory changes, and destruction of the nerve architecture.
- Leprosy have decreased but remains in areas of **poverty**.
- **Transmission**: **prolonged contact** with the patient. For example, areas with poverty are crowded which facilitates transmission.
- **Treatment**: Hansen's disease is treated with **multidrug therapy** (MDT) using a combination of antibiotics depending on the form of the disease (curable).
- Besides the obvious clinical symptom (disfigurement), we can diagnose the disease by
    a. **TISSUE BIOPSY**: from the skin, under the microscope using acid-fast stain (to confirm the diagnosis).
    b. history
- However, culture is not used because it takes very long time, and in the case of M.leprae, it won't even colonize **:(** Also, serology is not used because of no specific antibodies for M.leprae **:(**
- **Leprosy has affected humanity for thousands of years.**

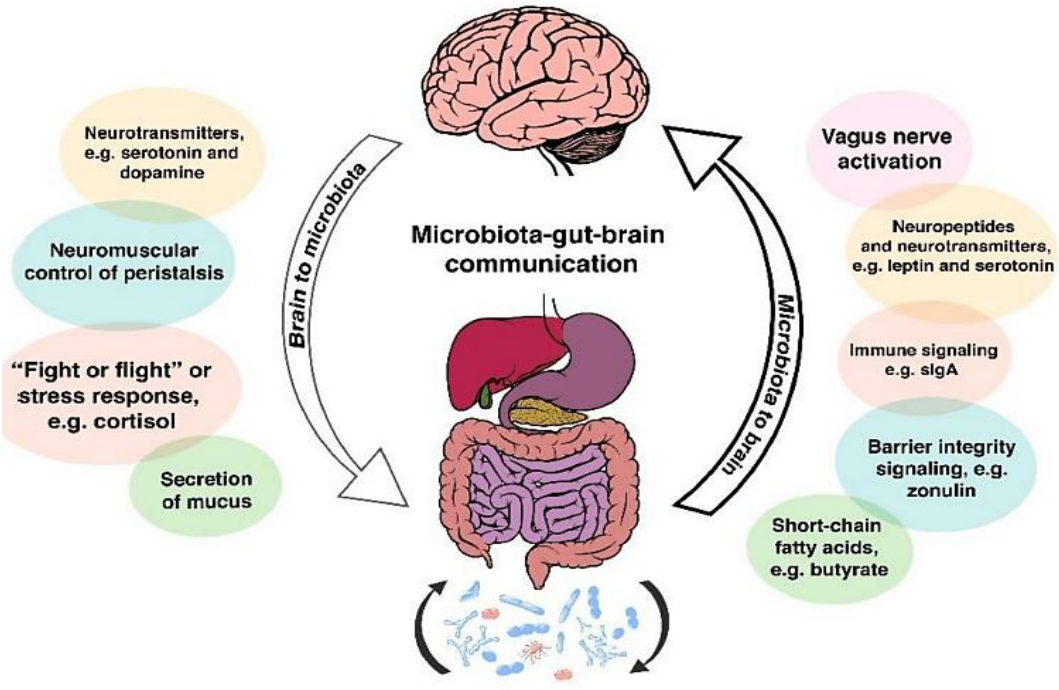
Spinalonga on Crete, Greece, one of the last leprosy colonies in Europe, closed in 1957.

- **Leper colonies (people with leprosy lived together in a colony,isolated from the rest of the world) or houses** became widespread in the Middle Ages, particularly in Europe and India, and were often run by monastic orders. Historically, leprosy has been greatly feared because it causes visible disfigurement and disability, was incurable, and was commonly believed to be highly contagious. A leper colony administered by a Roman Catholic order was often called a lazar house, after Lazarus, the patron saint of people affected with leprosy.
- Fortunately, due to antimicrobials and better lifestyle, there was a significant decrease in the number of cases.

GUT-BRAIN AXIS

- Basically, the microbiota that lives in your gut, apparently affects your mood and your CNS in general. The brain also exerts some effects on your intestines through secretion of mucus, peristalsis,and secretion of neurotransmitters, which will affect **the microbial diversity and relative abundance**. A new area of research where bacteria are given to alter the microbiota, which will affect the brain. For example, when lactobacilli were given to mice, the mice expressed less symptoms of autism.

microbial diversity affects CNS and vice versa.



Microbial diversity and relative abundance

JUST READ the rest as it will be discussed later on.

The gut-brain axis (GBA) consists of bidirectional communication between the central and the enteric nervous system, linking emotional and cognitive centers of the brain with peripheral intestinal functions. Gut microbiota seems to influence these interactions. 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 behavior and potentially affecting the onset and/or severity of nervous system disorders. Most of the data have been acquired using technical strategies consisting of germ-free animal models, probiotics, antibiotics, and infection studies. 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.

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

Strong evidence suggests that gut microbiota has an important role in bidirectional interactions between the gut and the nervous system. It interacts with CNS by regulating brain chemistry and influencing neuro-endocrine systems associated with stress response, anxiety and memory function. Many of these effects appear to be strain-specific, suggesting a potential role of certain probiotic strains as novel adjuvant strategy for neurologic disorders. In addition, the effects of CNS on microbiota composition are likely mediated by a perturbation of the normal luminal/mucosal habitat that can also be restored by the use of probiotics and possibly by diet. In clinical practice, an example of this interaction is constituted by Functional gastrointestinal disorders, in particular IBS, now considered a microbiome-GBA disorder.

THANK YOU