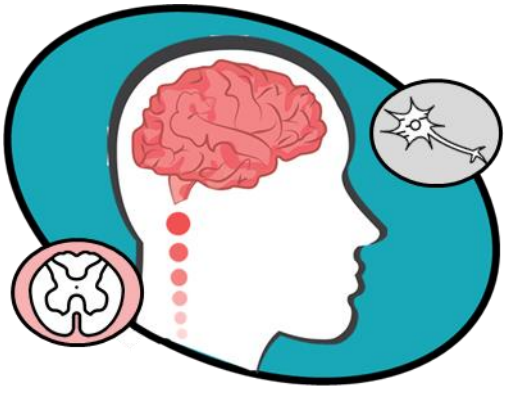

CNS

Microbiology

Sheet Slide

Number

4 (online lecture)

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Note: there is no need to return back to slides since everything is written here.

This sheet will cover three topics:

1.Encephalitis

2.Transmissible Spongiform Encephalopathies

3.Infectious Myelopathies

*Encephalitis

Encephalitis is an inflammation of the brain parenchyma that arises from penetration of the blood–brain barrier or overlying meninges. We came across this word previously when we talked about meningitis (we said that it is not uncommon for encephalitis to accompany meningitis and we called that condition "Meningoencephalitis"). **Meningitis is more common than encephalitis** and this makes sense; the meninges protect the brain and limit pathogen entry to the brain parenchyma.

Encephalitis patients present with signs and symptoms of brain dysfunction (altered or depressed level of consciousness). The pathogens can reach to the brain parenchyma via several different routes:

1) Haematogenous spread (like meningitis)

2) Direct spread (like meningitis)

3) ***Viruses*** (most commonly) invade the **sensory/motor nerve endings** and from there move to the CNS (e.g. (HSV or VZV) infects the epithelium of the skin, then the infection reaches the CNS via the sensory nerves -> the infection is "cured", but the virus hides in the dorsal root ganglia of the PNS -> upon reactivation of the virus the same previously infected areas get re-infected, that is the skin and the CNS).

Herpes Simplex Virus (HSV) is the most common cause of encephalitis, but still HSV infections rarely cause encephalitis because infecting the CNS would often lead to the death of the patient and this is an unpleasant scenario for the virus itself as it loses its host and therefore, loses its ability to reproduce, which is why encephalitis is a rare condition.

Both HSV I and II have the ability to cause encephalitis, but **HSV I infections are more common than HSV II infections.**

Rabies and polio viruses can also cause encephalitis, but by invading **motor neurons** rather than sensory ones (so they first infect the skeletal muscles and then invade the motor nerves via the neuromuscular junction).

HIV and SIV (Simian immunodeficiency virus) are capable of infecting the endothelium of the blood vessels, entering to the blood and from there reach the brain parenchyma (hematogenous spread).

In encephalitis the damage caused to the brain parenchyma is not only caused by the invading virus; the inflammatory response(neutrophils) initiated by the immune system can also damage the neurons of the brain. The microglial cells (resident macrophages of the CNS) for example, get activated when they engulf the viral protein (or neurotoxin) and in their activated state, the microglial cells are capable of damaging the neurons and activating the astrocytes which in turn release cytokines that end up increasing the damage even more.

Presentation

The patient usually comes with:

- Fever
- Headache
- Meningeal signs (in meningoencephalitis) (neck stiffness, positive Kernig's test and positive Brudzinski sign).
- Altered level of consciousness (hallucinations, agitation, personality change, behavioural abnormalities)
- Depressed level of consciousness ranging from mild lethargy (tiredness) to coma.
- Seizures (focal or generalised)
- Focal or diffuse neurological signs (e.g. cerebral nerve palsies)
  →Weakness in muscles on one side of the body
  →Aphasia and ataxia

Some viruses tend to infect certain areas more than others (e.g. **HSV tends to infect the temporal lobe**) and the symptoms will be related to the infected area. However, knowing the infected area is not sufficient to pin-point the causative agent, other tests are required (the virus

might also infect other areas, it's simply that this area is more commonly affected, and we can't take risks in a serious situation like encephalitis!).

Causative Agents

Despite comprehensive diagnostic efforts, the majority of cases of acute encephalitis of suspected viral etiology **remain of unknown cause.**

Many viruses can cause encephalitis, but the most commonly identified viruses causing **sporadic cases** of acute encephalitis in immunocompetent adults are **herpesviruses** (HSV, VZV, EBV).

For **epidemics**, the most common causative agents are **arboviruses** (viruses that are transmitted by arthropod vectors).

Since 2002, West Nile Virus was behind most of the encephalitis epidemics in the US. It is transmitted by mosquitos and has a reservoir in birds; humans are the dead-end hosts of WNV (if I got it right, then this mean that humans get infected by WNV, but do not transmit it).

Rabies

This is a disease caused by Rabies Virus and within the effects of the disease, encephalitis can develop.

The transmission of this virus is usually **zoonotic**, more specifically through a **bite** of a carnivore "dogs for example" or via bats.

After the initial exposure of the patient to the virus, the virus incubates within the patient's body for a period of days to months (must be less than a year). As mentioned previously, the Rabies virus reaches the CNS via the motor neurons.

Some special symptoms of Rabies infections include episodes of **hyper-excitability** followed by periods of **complete Lucidity** (calmness).

If the infection has reached the brain, then it is too late to save the patient and death is expected within days. Therefore, if a patient comes after being bitten (e.g. by a dog) and we suspect the dog to be infected by Rabies we begin with **post-exposure prophylaxis** [**taking care of the wound** by cleaning it thoroughly to avoid the spread of the virus and giving **passive immunisation** to the patient (**antibodies against Rabies**)] and then all we can do is wait and hope that the disease doesn't spread as there is still a chance for that to happen.

Under the microscope, we see eosinophilic cytoplasmic bodies (**Negri bodies**) within the brain neurons. These Negri bodies look similar to parasites and therefore, the disease was initially thought to be caused by parasites.

CLINICAL STAGES OF RABIES

PHASE	TYPICAL DURATION	SYMPTOMS AND SIGNS
Incubation period	20–90 days	None
Prodrome	2–10 days	Fever, malaise, anorexia, nausea, vomiting; paresthesias, pain, or pruritus at the wound site
Acute neurologic disease		
Encephalitic (80%)	2–7 days	Anxiety, agitation, hyperactivity, bizarre behavior, hallucinations, autonomic dysfunction, hydrophobia
Paralytic (20%)	2–10 days	Flaccid paralysis in limb(s) progressing to quadriparesis with facial paralysis
Coma, death[a]	0–14 days	

[a]Recovery is rare.
Source: MAW Hattwick: Rabies virus, in Principles and Practice of Infectious Diseases, GL Mandell et al (eds). New York, Wiley, 1979, pp 1217–1228. Adapted with permission from Elsevier.

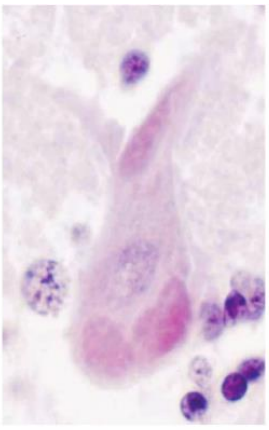


FIGURE 105-3
Three large Negri bodies in the cytoplasm of a cerebellar Purkinje cell from an 8-year-old boy who died of rabies after being bitten by a rabid dog in Mexico. (From AC Jackson, E Lopez-Corella: N Engl J Med 335:568, 1996. © Massachusetts Medical Society.)

Diagnosis of Encephalitis

***A lumbar puncture** is performed to get a CSF sample. In case of a positive result then we expect to see increased lymphocytes **(lymphocytes pleocytosis), mildly elevated proteins** and a **normal glucose concentration**. These findings are pretty similar to those of meningitis.

***PCR** can be done on a CSF sample to look for viral DNA/RNA.

Serology**: Anti-WNV IgM antibodies can be used in epidemics ***and a positive result is diagnostic for WNV encephalitis.

***Neuroimaging**: can help identify or exclude alternative diagnoses (such as tumors) and assist in the differentiation between focal, as oppose to a diffuse, encephalitic process.

In case all of the previous tests fail and the patients condition is continuously deteriorating, then we are left with no choice, but to take a ***brain biopsy**.

Treatment:

In the initial stages of encephalitis, many patients will require care in an **intensive care unit (ICU)**. Basic management and supportive therapy should **include careful monitoring of vital signs and ICP (intracranial pressure).**

*** Acyclovir** is of benefit in the treatment of HSV (and VSV and EBV severe infections) and should be **started empirically** in patients with suspected viral encephalitis, while awaiting viral diagnostic studies.

* There is considerable variation in the incidence and severity of sequelae in patients surviving viral encephalitis. Many patients with **WNV infection have sequelae, including cognitive impairment; weakness**; and hyper- or hypokinetic **movement disorders**, including tremor, myoclonus, and parkinsonism.

Prion diseases

Prions are misfolded infectious proteins. These proteins are normally secreted by the healthy neurons and they have specific functions in the cell, but if they happen to get misfolded then they become prions and can infect (misfold) other normal proteins. All these misfolded proteins accumulate inside the cell and eventually cause its death. This means that prion diseases cause slow degeneration of the brain and can therefore be grouped under the neurodegenerative diseases.

The Transmissible Spongiform Encephalopathies (TSEs) are diseases that occur due to prions formation and they are called “Spongiform” because when the cerebral cortex and the cerebellum get degenerated, the remaining tissue looks like a sponge.

There are 3 major **human** diseases in the TSE family:

1- Creutzfeldt-Jacob disease (CJD) (4 forms):
   -the sporadic (sCJD) - the hereditary/familiar (fCJD) - the iatrogenic (iCJD) - the variant form (vCJD).
2- Kuru (has become pretty rare).
3- Fatal Familial Insomnia(FFI).

The CJD is the most common of these diseases. The Kuru disease was found in a tribe that practiced ritualistic cannibalism, where the tribe members ate the brains of their dead relatives…

There are two more diseases in the TSE family, but they only affect the **animals**:

1- Scrapie (affects sheep and goats)
2- Bovine Spongiform Encephalopathy (BSE) (Madcow disease, affects cows)

The first ever prion was discovered in the brain of a sheep affected with Scrapie. It is thought that the development of the BSE related to the food given to the cows as they were given mashed remnants of other cows…

Forms of Creutzfeldt-Jacob Disease

1) **Sporadic**; the infectious prions are believed to be made by an **error of the cell machinery** that makes proteins and controls their quality. These errors are more likely to occur with **aging**, which explains the general advanced age at onset of CJD and other prion diseases.

2) **Familial**; If the prion protein gene is altered in a person's **sperm or egg** cells, the mutation can be transmitted to the person's offspring. The particular mutation found in each family affects **how frequently the disease appears and what symptoms are most noticeable.**

3) **acquired (iCJD)/(vCJD)**

• **Iatrogenic**: Accidental transmission o CJD to humans appears to have occurred with **corneal transplantation, contaminated (EEG) electrode implantation, and surgical procedures**.

• **Variant**: Acquired by **eating meat** from cattle affected **by BSE,"mad cow" disease.**

Signs & Symptoms of CJD

The signs and symptoms of CJD reflect the degeneration of the brain:

*rapidly progressing dementia(confusion, disorientation, and problems with memory, thinking, planning and judgment).

*Rigidity

*myoclonus

* at later stages: ataxia, gaits and speech impairment.

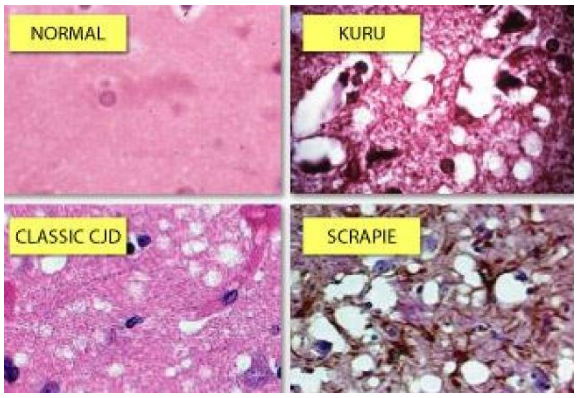
From slides:

Myoclonus: is a brief, involuntary twitching of a muscle or a group of muscles caused by sudden muscle contractions (positive myoclonus) OR brief lapses of contraction (negative myoclonus). • Most patients (90%) with CJD exhibit myoclonus that appears at various times throughout the illness. • Myoclonus persists during sleep, Unlike other involuntary movements.

How is CJD diagnosed?

• **Electroencephalography (EEG)** : can be particularly valuable because it shows a specific type of abnormality in major but not all types of CJD.

• **Magnetic resonance imaging (MRI)** :has recently been found to be accurate in about 90 percent of cases.



• The **only way to confirm a diagnosis of CJD is by brain biopsy or autopsy**.

In a brain biopsy, a neurosurgeon removes a small piece of tissue from the person's brain so that it can be examined by a neuropathologist.

Unfortunately, there is **no treatment** till now for this disease, therefore, all we can do is give a **palliative** treatment to the patient, that is to improve their quality of life and help them overcome their physical and mental struggles.

Opiate drugs can be given just to relieve the **pain** and **Clonazepam and Sodium Valproate** can be given to relief **myoclonus** (just symptomatic treatment...).

Spinal Cord Infections

We are going to briefly discuss the infections of the spinal cord (a.k.a infectious myelopathies or myelitis) which are very rare conditions.

Herpesviruses and enteroviruses are the most common causative agents of myelitis.

The symptoms depend on which level of the spinal cord the infection occurred at (because the infection will affect the nearby spinal nerves).

The disease can also be caused by bacteria (e.g. staph aureus), it then becomes a space occupying lesion and an abscess can form (e.g. an epidural abscess between the dura matter and the spinal vertebrae can form). An inflammation can accompany the abscess.

Myelopathies can also be expected at late stages of syphilis (secondary or tertiary syphilis) (T. Pallidum), but this is very rare as syphilis gets treated at an early stage nowadays.

GOOD LUCK (: