Lecture out line: Virus Infections of the CNS - 2019

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25.02.2019

Infections of the CNS

Infection of the central nervous system (CNS) can be viral, bacterial, fungal, or parasitic in origin.

Fortunately, CNS infections are uncommon due to blood brain barrier (blood –CSF barrier).

Types of CNS infections:

Once infectious agents enters the CNS neurological disease results, involving

(i). Meningies – meningitis.

Viral meningitis is the commonest. Bacterial meningitis is the next common. Acute meningitis (purulent or aseptic) and Chronic meningitis

(ii). Brain substance - encephalitis - viral encephalitis, Encephalopathy (scrapie, CJD, kuru)

(iii). Brain & meningies - Meningoencephalitis

(iv). Brain/Cerebral abscesses

(v). Spinal cord - myelitis occasionally affected

(vi). Peripheral nerves - neuritis

Pathogenesis of CNS infections:

(a). Routes of CNS infections:

(1). Blood borne

(i). Blood-brain Barrier: endothelial cells not fenestrated. Thick basement membrane, astrocytes lining the blood vessel

(ii). Blood-CSF Barrier: endothelium fenestrated. Thin basement membrane, Choroid plexus epithelium lining the blood vessel

2. Via peripheral nerve tracts

3. Local invasion:

Infectious microorganisms most often enter the CNS by direct penetration after trauma or by travelling in the bloodstream.

Disease results from

(i). Interference of function of infected nerve cells. i.e. rabies

(ii).Direct damage to infected nerve cells. i.e. poliomyelitis

(iii). Inflammatory sequel to CNS infection. i.e. bacterial meningitis, viral encephalitis

(iv). Bacterial neurotoxins reach the CNS from

extra neural sites of growths →i.e. tetanus,

contaminated food →i.e. botulism

Invasion of the CNS - Mechanisms and examples

1. Via Blood-brain barrier.
   i.e. viruses (Poliovirus, Mumps virus)
   Bacteria (*Haemophilus influenza*, Meningococci, Pneumococci
2. Invasion via peripheral nerves. i.e., viruses (HSV, VZV, Rabies virus)

Response to invasion:

(a). Invading virus → *Aseptic meningitis:*

(i). Increased T cells in CSF (T cells and monocytes)

(ii). Slightly increased proteins in CSF

(iii). CSF remains clear

(b). ***Pyogenic bacteria*** → *Septic meningitis*

(i). Increased PMN in CSF

(ii). Increased protein in CSF

(iii). CSF become turbid

(c). Less pyogenic microorganisms less dramatic: i.e. MTB, Listeria

1. CSF Normal values (Sterile)

{Conversions: *1 microliter (μl) = 1mm^3,* ***1ml = 1cm^3 = 1000 microliter (1ml), 100 ml = 1dl}***

(i). Appearance → water clear

(ii). Cells→ No more than 5 lymphocytes/ μl

(iii). Protein concentration → 15-45mg/dl

(iv). Glucose concentration → 45- 85mg/dl (depend on level of blood glucose)

2/3 blood glucose = CSF glucose level (<50% blood glucose level = decreased CSF glucose level)

Normal glucose range = non-diabetic patient

Important to have knowledge on blood glucose level before making any assessment on CSF glucose level.

(*The international standard way of measuring blood glucose levels is in terms of a molar concentration, measured in mmol/L (millimoles per litre; or millimolar, abbreviated mM).*

The body's homeostatic mechanism of blood sugar regulation (known as glucose homeostasis), when operating normally, restores the blood sugar level to a narrow range of about 4.4 to 6.1 mmol/L (79 to 110 mg/dL) (as measured by a fasting blood glucose test).[6]

The normal blood glucose level (tested while fasting) for non-diabetics, should be between 3.9 and 5.5 mmol/L (70 to 100 mg/dL). The mean normal blood glucose level in humans is about 5.5 mmol/L (100 mg/dL);[5] however, this level fluctuates throughout the day. Blood sugar levels for those without diabetes and who are not fasting should be below 6.9 mmol/L (125 mg/dL).[7] The blood glucose target range for diabetics, according to the American Diabetes Association, should be 5.0–7.2 mmol/l (90–130 mg/dL) before meals, and less than 10 mmol/L (180 mg/dL) after meals (as measured by a blood glucose monitor).

2. CSF values during – Septic / purulent bacterial meningitis:

(i). Appearance= cloudy or turbid

(ii). Cells (high)→ 200-20000 PMN/(μl) cells almost all Neutrophils (~ 90%)

(iii). Protein value increased >100mg/dL

(iv). Glucose value decreased <45 mg/dL (relative to blood glucose)→ very low

Causes of Septic / purulent meningitis: i.e. Bacteria, Amoeba & Brain abscess

3. CSF values during - Aseptic meningitis or Meningoencephalitis or viral encephalitis

(Aseptic because CSF is sterile on regular bacteriological culture).

(i). CSF is clear. i.e. Viruses & Certain slow growing and less pyogenic organisms.i.e., TB, Leptospira, Listeria, Fungi, partly treated bacterial meningitis

(ii). WBC→ 100 -1000/ml (mainly mononuclear/lymphocytes) mononuclear cells predominate, PMN may be present even predominate at the onset

(iii). Glucose value → normal in the viral cases (45-85/mg/dL) or low (<45mg/dL) in the case of tuberculosis, fungi and leptospira

(iv). Protein value→normal or slightly elevated (50-100mg/dL)

4. CSF values during – TB

(i). Cells (raised)→200-2000 lymphocytes/ml (almost all lymphocytes)

(ii). Glucose value decreased (relative to blood glucose)→ low

(iii). Protein value increased

Pathological consequences of CNS infection by viruses:

Virus induced peri-vascular infiltration of lymphocytes and monocytes (PVC)

Direct damage to cells in poliovirus infection (Lytic)

Immunity: **B cells** → antibody, **T cells** → cytokines

<u>Viral meningitis</u>

Much more common than bacterial meningitis

Milder than bacterial meningitis

Headache, fever, photophobia but less neck stiffness

CSF clear in the absence of bacteria

Cells are mainly lymphocytes although PMN may be present in early stages.

Virus can be isolated in <50% of cases therefore, virus genome detection (PCR) methods used in the diagnosis

Causes of viral meningitis include five groups of human enteroviruses: *Coxsackie group A and B viruses, echoviruses and three polio viruses.*

Commonly asymptomatic, so enterovirus isolated from throat or stool of a child with mild meningitis

Viruses are common causes of seasonal aseptic meningitis

Viral meningitis has a benign course and complete recovery is the rule

Causes of viral meningitis

1. Mumps (a common complication)
2. HSV (uncommon, may follow genital infection)
3. Lymphocytic choriomeningitis (LCM) (uncommon infection from urine of mice, hamsters carrying virus)
4. JE (Sri Lanka, India, South East Asia, Japan)
5. WEE (West USA) & EEE (East USA)
6. Louping ill (Scotland)
7. HIV (may occur early after infection)

Viral meningoencephalitis: Epidemiology

Enteroviruses: Seasonal → common in summer & tropical countries

Arboviruses:	Seasonal	→ common in summer & tropical countries
Mumps:	Seasonal	→common in winter & spring
LCMV:	Seasonal	→ common in winter & spring
HSV:	No seasonal pattern	

Infectious causes of Encephalitis:

(i). Viruses (sporadic occurrence) – HSV, Mumps, VZV, CMV, Rabies, Louping ill, HIV

(ii). Viruses (may be outbreaks)- polio & other enteroviruses, Togaviruses (EEE & WEE, St Louis encephalitis virus, JE, Californian encephalitis virus)

(iii). Slow viruses: - Rubella, measles, JC virus

(iv). Prions (non-viral)

(v). Post vaccinal or post viral ?

Enteroviral infections - Polio viruses:

A common cause of encephalitis.

Three serologic (antigenic types of polio viruses with little cross reaction.

~ 75% of paralytic cases are due to type 1 polio virus.

CNS disease occurs in <1% of those infected

Fever for 1-4 days, sore throat & malaise and meningeal signs and symptoms appear followed by involvement of motor neurons and paralysis.

Successful vaccines available: Oral polio (Sabin vaccine) & inactivated vaccine (Salk vaccine)

EPI programme of Sri Lanka: 5 doses of OPV vaccinations at 2, 4, 6, 18 months, and at 5 years

Global Polio Eradication Initiative reduced number of polio endemic countries from 20 to 10 during 2001 and 2002

<u>Other Enteroviruses</u>

Coxsackie viruses (group A and B), Echoviruses, Enterovirus 71

Mostly children under 5years of age

Treatment is supportive

There is no vaccine

Occasionally cause meningoencephalitis

Paramyxovirus infections

<u>(i). Mumps:</u>

A common cause of mild encephalitis.

Asymptomatic CNS invasion may be common. Increased number of cells in CSF of 50% patients with parotitis.

Meningitis and encephalitis often seen without encephalitis.

(ii). Nipah virus encephalitis:

An emerging zoonotic paramyxovirus infection

1st reported among pig farm workers in Malayasia in1998- 105 deaths among 265 patients

Transmission to humans by close contact with infected pigs by aerosol

Outbreak was ended by culling 1 million infected pigs local and surrounding regions.

Malayasia's flying fox (*Pteropus hypomelanus*) a fruit bat was likely reservoir- virus could be found in urine & saliva of infected bats

Pigs infected by feeding on food contaminated with fruit bat secretions.

(iii). Rabies encephalitis

35000 cases of human rabies worldwide mostly due to dogs.

More than 1 million deaths per year in cattle due to vampire bats

Etiology of rabies

Caused by rabies virus belongs to Genus Lyssavirus of family Rhabdoviridae

Genus Lyssavirus has been classified into genotypes –

genotype	**Host**
1. rabies (RAB – classical)	Warm blooded animals
2. lagos bat (LB)	bat, cat
3. Mokola (MOK)	shrew, dog, cat, man, rodent
4. Duvenhage (DUV)	bat
5. Europian bat virus type 1 (EB-1)	bat
6. Europian bat virus type 2 (EB-2)	bat
7. Australian bat lyssavirus	bat
8. Gannoruwa bat lyssavirus	bat (recent finding from Gannoriwa, Peradeniya, Sri Lanka)

Transmission of rabies virus:

Virus is excreted in saliva of infected dogs, foxes, jackals, wolves, skunks, raccoons, vampire and other bats.

Can infect all warm-blooded animals.

Transmission to humans via bite or salivary contamination of skin abrasions, wounds, mucous membranes

Some species are more infectious than others –large amount of virus 10^6 infectious doses/ml

Apparently healthy dog is still healthy 10 days after biting a human, rabies is extremely unlikely.

Virus can be excreted in dog's saliva before the animal show any clinical signs of rabies

Incubation period: 4-13 weeks, as long as 6 months.

Distal the bite from CNS, longer the incubation period

Laboratory diagnosis of rabies:

(i). Detecting viral antigen by IF

(ii). Detecting viral RNA in skin biopsies, corneal impression smears, brain biopsy by PCR

(iii). Detecting Negri bodies (intracytoplasmic inclusion bodies) in neurones by Sellar's stain

Control of rabies

(i). Vaccination of the reservoir (dog)

(ii). Vaccination of wild foxes by dropping food baited with live virus vaccine from the air

Rabies free countries constant vigilance at borders, strict quarantine regulations. i.e., England is a rabies free country. Rabies was endemic in England in 1886 -36 human deaths (11/36 from London)

In Sri Lanka rabies endemic in all provinces and 51 human deaths occurred in 2012. Refer to latest figures of rabies deaths in Sri Lanka -2015, 2016, 2017

Rabies -Prevention

After exposure to a suspected rabid animal – Immediate prevention action to be taken.

If PEP started as early as possible chances of prevention greater.

Prompt cleaning of the wound (soap and running water & alcoholic iodine, debridment)

Confirmation of whether or not animal is rabid (clinical observation of suspected dog, Histology for Negri bodies, Ag detection by IF & Other species by histology, IFAg, PCR)

Prompt passive immunization (Administration of RIG- half dose to wound and half IM)

Active immunization with anti-rabies vaccine (inactivated cell culture grown virus vaccine)

Risk of getting rabies

Risk is greater if

1. High dose of virus inoculated- deep bites, multiple bites

2. Site of bite is closer to CNS or highly innervated, i.e., head, face, finger tips, genitalia

3. Contamination of mucous membranes

4. Bare skin rather than clothed

Other Viral causes of encephalitis

Varicella-zoster virus

Post infectious encephalitis (after chicken pox)

Zoster encephalitis as a complication of herpes zoster

HSV 1 & 2:

The commonest cause of sporadic viral encephalitis

Any age including newborn (neonatal herpes)

Manifestation of primary or more commonly secondary reactivated HSV infection

Diagnosis of Herpes simplex enecephalitis

Difficult. Relied upon following approaches in decreasing order of sensitivity.

1. Brain Biopsy: Clinicians feels that this invasive procedure cannot be justified

2. Clinical and neurological investigation. Mainstay of acute diagnosis if a brain biopsy is not performed.

Presence of a focal lesion seen by brain imaging is the most sensitive indicator of diagnosis of HSE other than brain biopsy.

3. Microbiological investigations

The demonstration of a rise in serum anti HSV antibody titres and of intrathecal synthesis of such antibodies.

Demonstration of intrathecal Abs requires both assay of anti-HSV in the CSF and simultaneous measure of blood- brain barrier function, usually provided by comparing blood and CSF anti HSV titires with blood and CSF albumin concentrations.

Drawback of this approach is it may take several days if not weeks for positive results.

Rapid virological disgnosis by PCR may be possible

Treatment for herpes simplex encephalitis (HSE)

It is vital that Specific antiviral therapy be started as soon as the diagnosis is suspected Any delay may have dire consequences in terms of residual morbidity on recovery

Immediate high dose of IV ACV for at least 10 days

Togavirus meningitis & encephalitis:

Many arthropod-born Togaviruses (WEE, EEE, JE, SLE) can cause meningitis and encephalitis

Cause outbreaks of encephalitis

Different parts of the world:

Different mammals, birds or even reptiles act as RESERVOIRS

Different arthropod vectors i.e. mosquitoes, ticks

JE endemic in Sri Lanka (Geographically localized

It is controlled in Sri Lanka due to effective JE vaccination under EPI (at 9 months of age)

(i). Japanese Encephalitis

Reservoirs of JE →Pigs

(ii). West Nile virus- emerging cause of encephalitis:

In 1999, epidemic of WNV encephalitis in New York city in 62 patients, 7 died.

There were deaths among wild birds – avian reservoir

WNV belongs to JE serogroups of flaviviruses that include JE, SLE.

Primarily a infection of birds and Culicine mosquites.

Humans and horses accidental hosts.

Diagnosis by detecting WNV RNA or IgM in serum or CSF

No vaccine. Only supportive treatment.

Retrovirus meningitis & encephalitis

HIV can cause sub-acute encephalitis with dementia

HIV invades CNS shortly after initial infection. Cause increased cells in CSF, mild meningitic illness.

Later stage independently if immune deficiency, develop sub-acute encephalitis often with dementia.

Difficult to differentiate from neurologic disease caused by microorganisms such as *T gondi, C neoformans,* CMV, JC virus,

Post vaccinial and post infectious encephalitis

Can occur following viral infections due to autoimmune responses. i.e. 1-2 weeks after measles, less commonly with VZV.

Inflammatory demyelinating condition of peripheral nerves knows as Guillain –Barre syndrome associated with several viral infections.

Measles virus invade CNS slow growth but incomplete after up to 10 years cause SSPE

Rubella occasionally cause SSPE like disease but more commonly like CMV invade brain of the fetus cause mental retardation.

Influenza virus: Post infectious encephalitis

Spongiform encephalopathies by prions

Scrapie type agents – host coded prion proteins infects mammals, including humans

Disease in animals seems to have originated from sheep and goats with scrapie for 200-300 years. sheeps srape against posts for relief.

December 2003: First U.S. Case Of Mad Cow Disease

Refer about **vCJD**