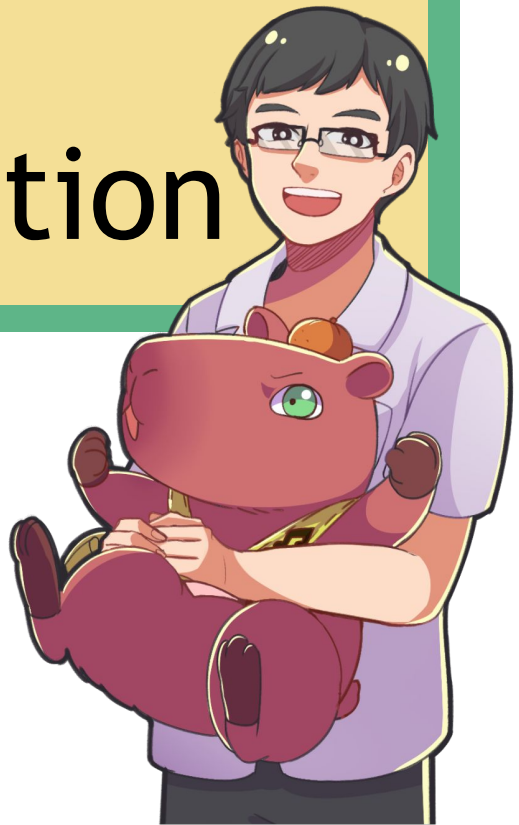
Clinicohistological approach in CNS infection



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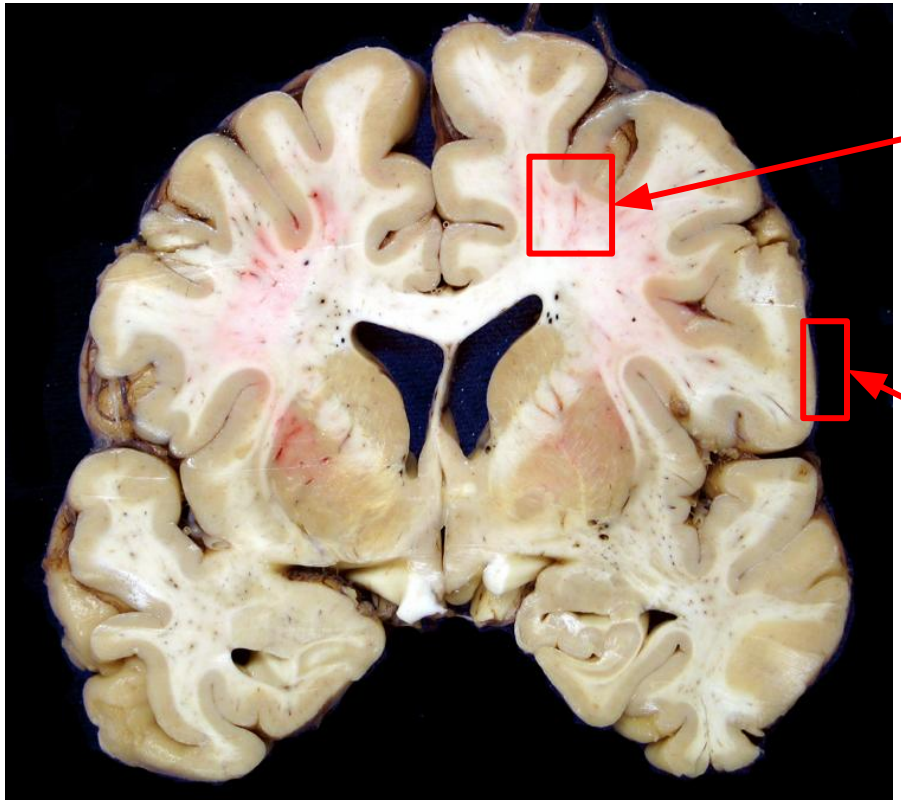
Advisor : Poosanu Thanapornsangsuth, M.D.

Outline

1. Basic anatomy and histology
    > Brain parenchyma
    > Meninges
2. General concept of CNS infection
3. Encephalitis
4. Brain abscess
5. Meningitis(Leptomeningitis)

Basic anatomy and histology

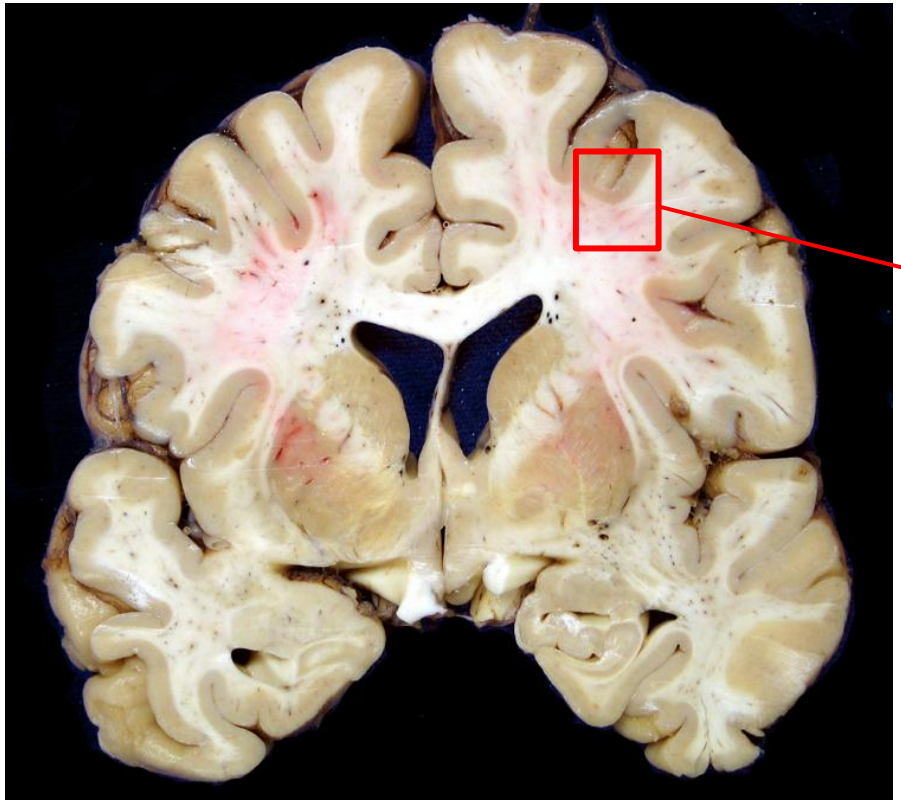


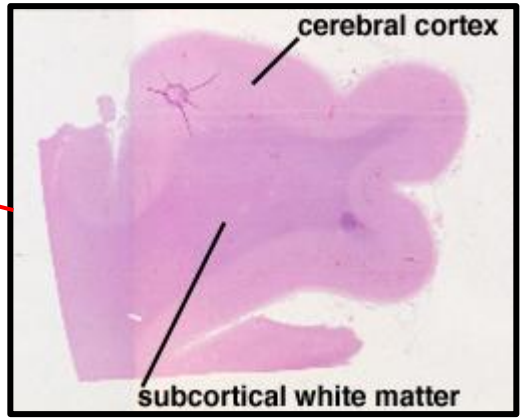
Brain parenchyma
- Cortical dysfunction
- Focal neurological deficit
- Seizure

Meninges
- Headache
- Nuchal rigidity
- Nausea/Photophobia
- Cranial neuropathy

Brat D. J.Normal Brain Histopathology. Practical Surgical Neuropathology. 2017;19-37

Brain parenchyma

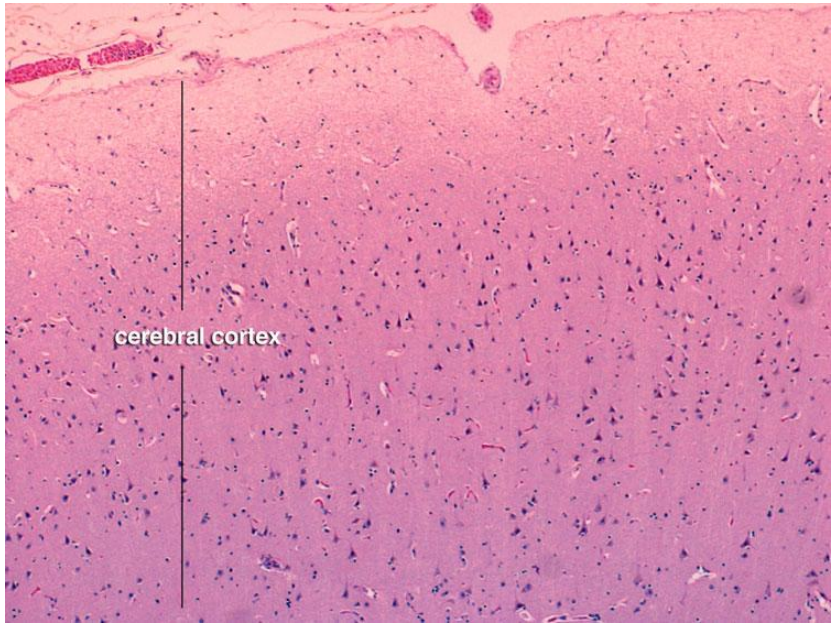


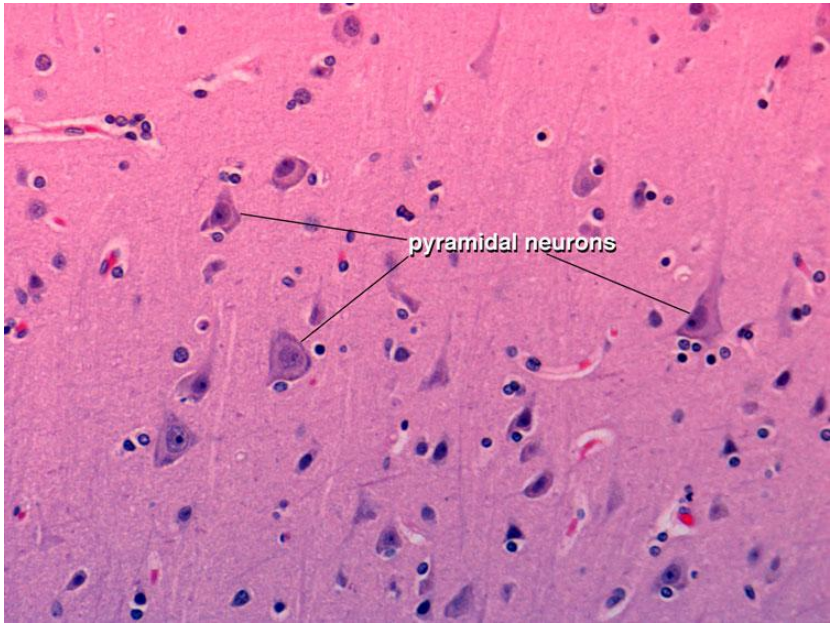


Brat D. J.Normal Brain Histopathology. Practical Surgical Neuropathology. 2017;19-37

Brain parenchyma

Cerebral cortex

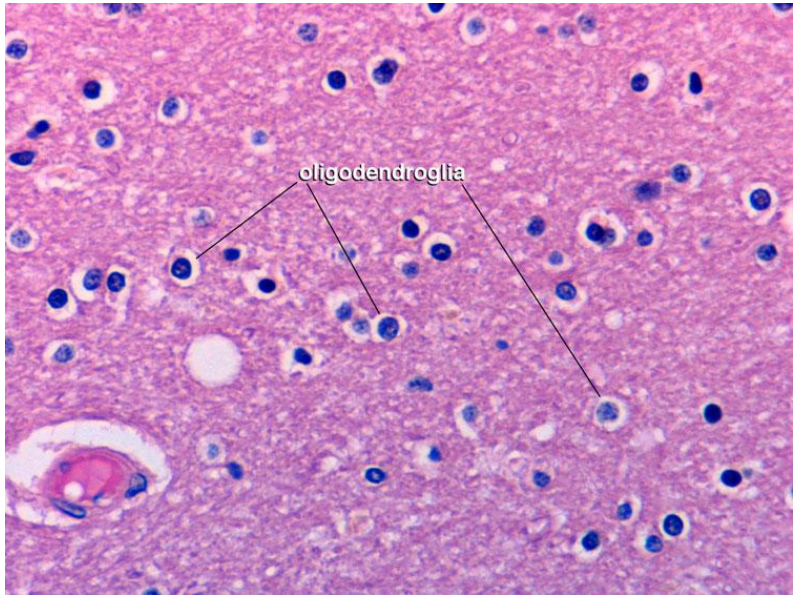


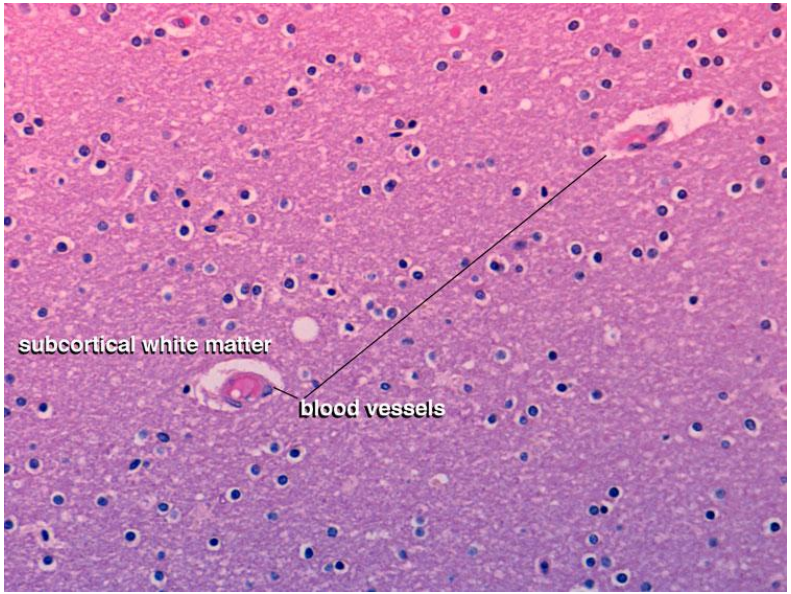


Brat D. J.Normal Brain Histopathology. Practical Surgical Neuropathology. 2017;19-37

Brain parenchyma

Subcortical white matter



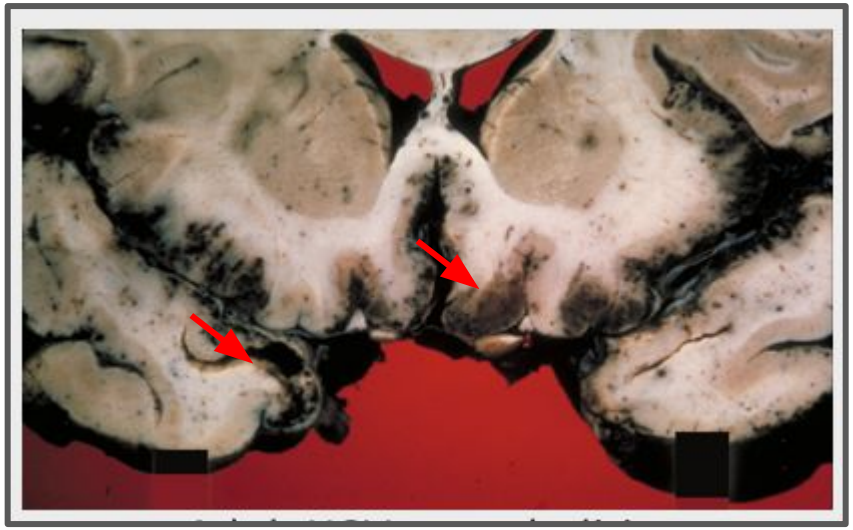


Brat D. J.Normal Brain Histopathology. Practical Surgical Neuropathology. 2017;19-37

Brain parenchyma

Encephalitis : Gross pathology

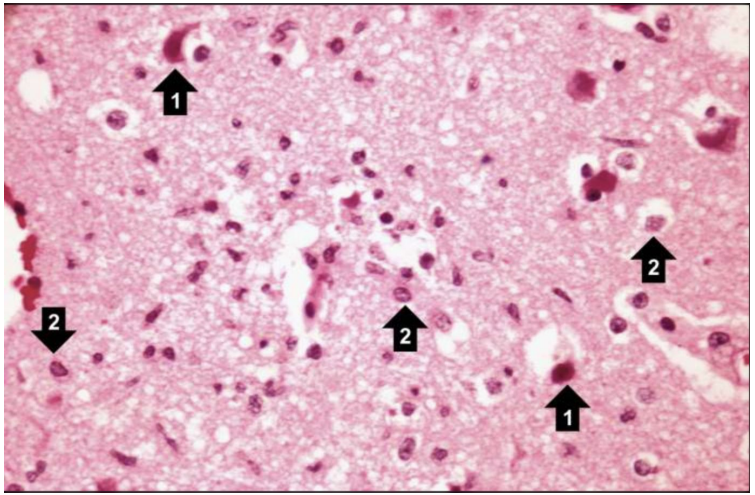
Show diffuse softening and edema, accentuated by hemorrhagic necrosis of the inferior frontal and temporal lobes



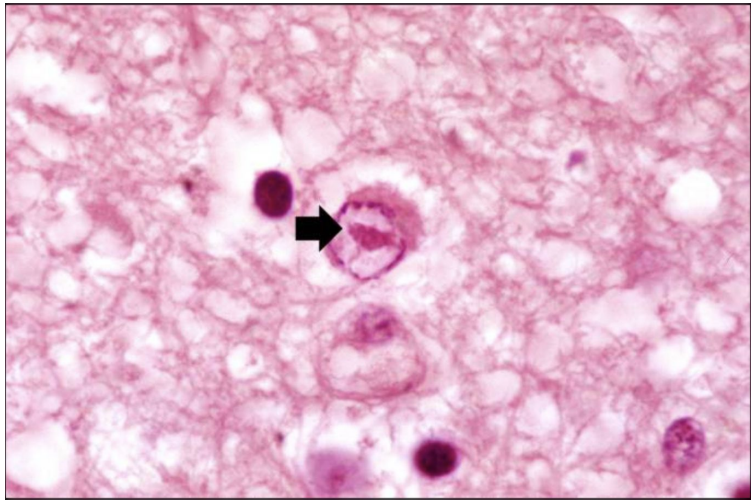
Kleinschmidt-DeMasters B. K., Keohane C. K.Herpes Simplex Virus Infections of the CNS.Infections of the Central Nervous System: Pathology and Genetics. 2020; 43-54

Brain parenchyma

Encephalitis : Histopathology



Demonstrating clear areas, which indicate edema, and
(1) Numerous shrunken red necrotic cells.
(2) Eosinophilic intranuclear inclusion bodies have displaced chromatin to the periphery of the nucleus in some cells

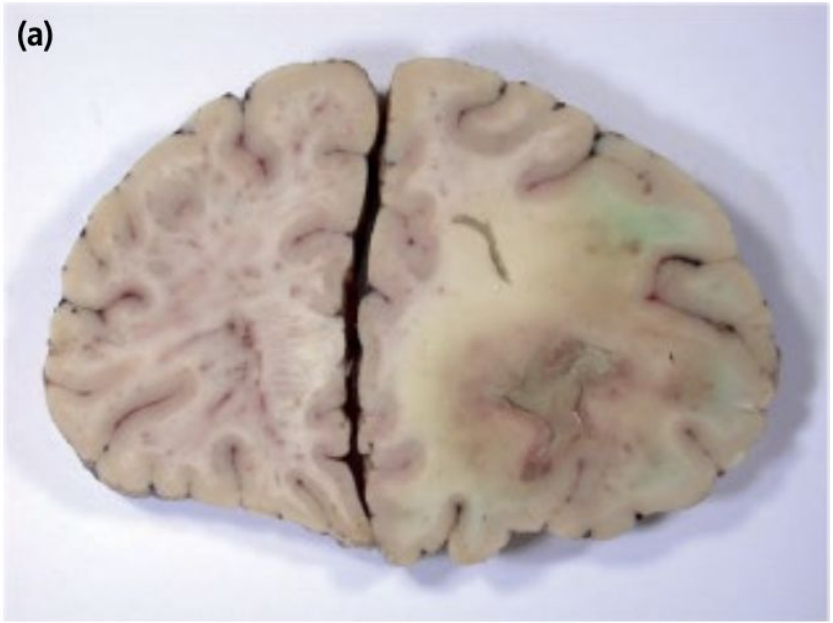


Cytopathic cell : a cell containing an intranuclear inclusion body

Kleinschmidt-DeMasters B. K., Keohane C. K.Herpes Simplex Virus Infections of the CNS.Infections of the Central Nervous System: Pathology and Genetics. 2020; 43-54

Brain parenchyma

Brain abscess : Gross pathology

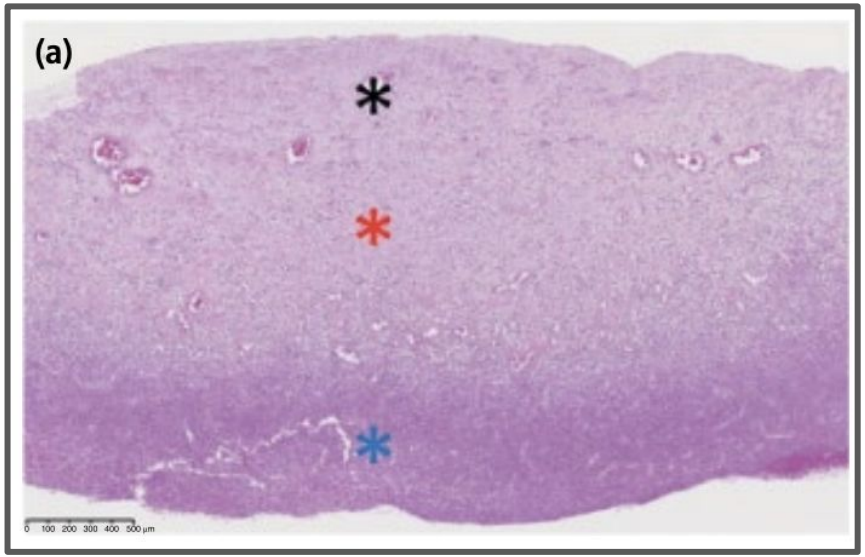


Focal necrotic lesion containing pus in its center in the white matter of the right frontal lobe, at the gray and white matter junction, surrounded by congestion.

Espariat A. T., Roux A. Pyogenic Infections of the CNS 2: (Brain Abscess, Subdural Abscess or Empyema, Epidural Abscess, Septic Embolism, and Suppurative Intracranial Phlebitis).Infections of the Central Nervous System: Pathology and Genetics. 2020; 309-18

Brain parenchyma

Brain abscess : histopathology

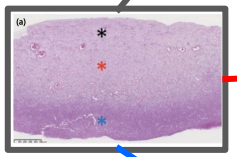


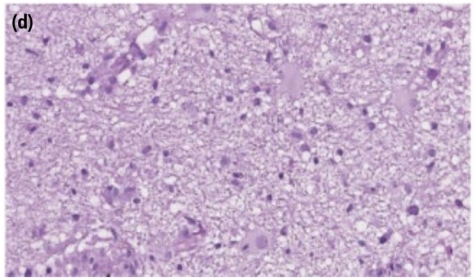
Low magnification showing different parts of the abscess:

(black asterisk)
An outer zone as the adjacent edematous brain parenchyma
(red asterisk)
The peripheral portion as granulation tissue the adjacent brain parenchyma
(blue asterisk)
the central portion as pus formation

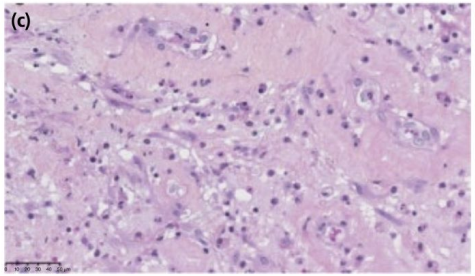
Espariat A. T., Roux A. Pyogenic Infections of the CNS 2: (Brain Abscess, Subdural Abscess or Empyema, Epidural Abscess, Septic Embolism, and Suppurative Intracranial Phlebitis).Infections of the Central Nervous System: Pathology and Genetics. 2020; 309-18

Brain parenchyma

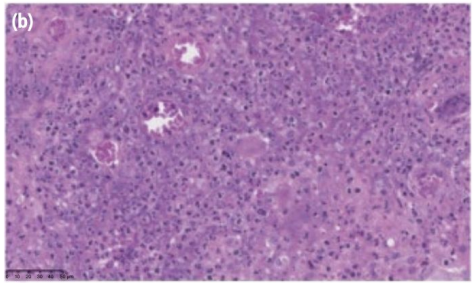




Outer zone of gliosis with reactive astrocytes and edema



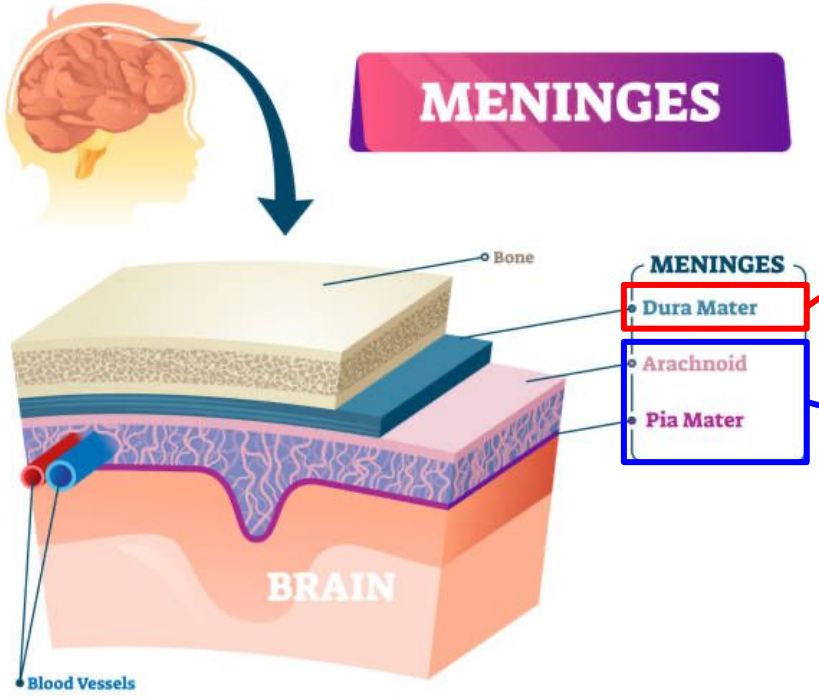
Surrounding inflammatory granulation tissue with vascular and fibroblastic proliferation and chronic inflammatory cells



Central portion with numerous polymorphonuclear leukocytes

Espariat A. T., Roux A. Pyogenic Infections of the CNS 2: (Brain Abscess, Subdural Abscess or Empyema, Epidural Abscess, Septic Embolism, and Suppurative Intracranial Phlebitis).Infections of the Central Nervous System: Pathology and Genetics. 2020; 309-18

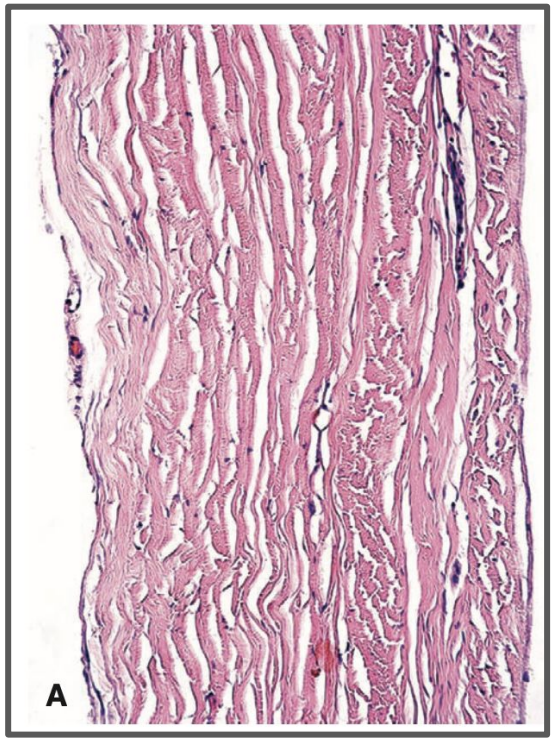
Meninges



Pachymeninges

Leptomeninges

Meninges



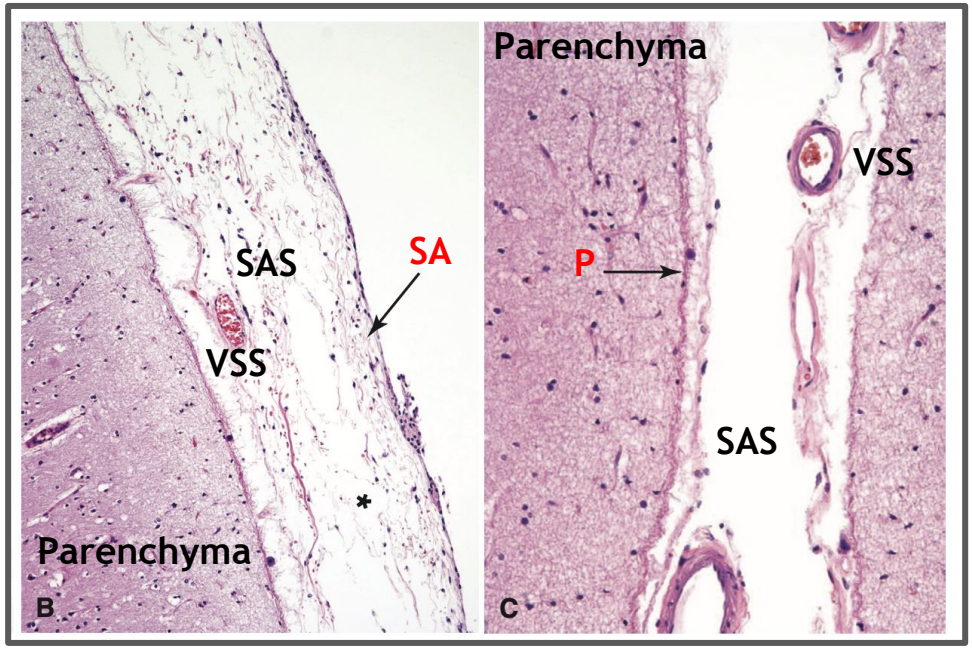
Pachymeninges

The dura mater is a thick, dense fibrous connective tissue covering for the brain with low cellularity.

Brat D.J. Normal Brain Histopathology.Practical Surgical Neuropathology, 2016; 19-37

Meninges

Leptomeninges



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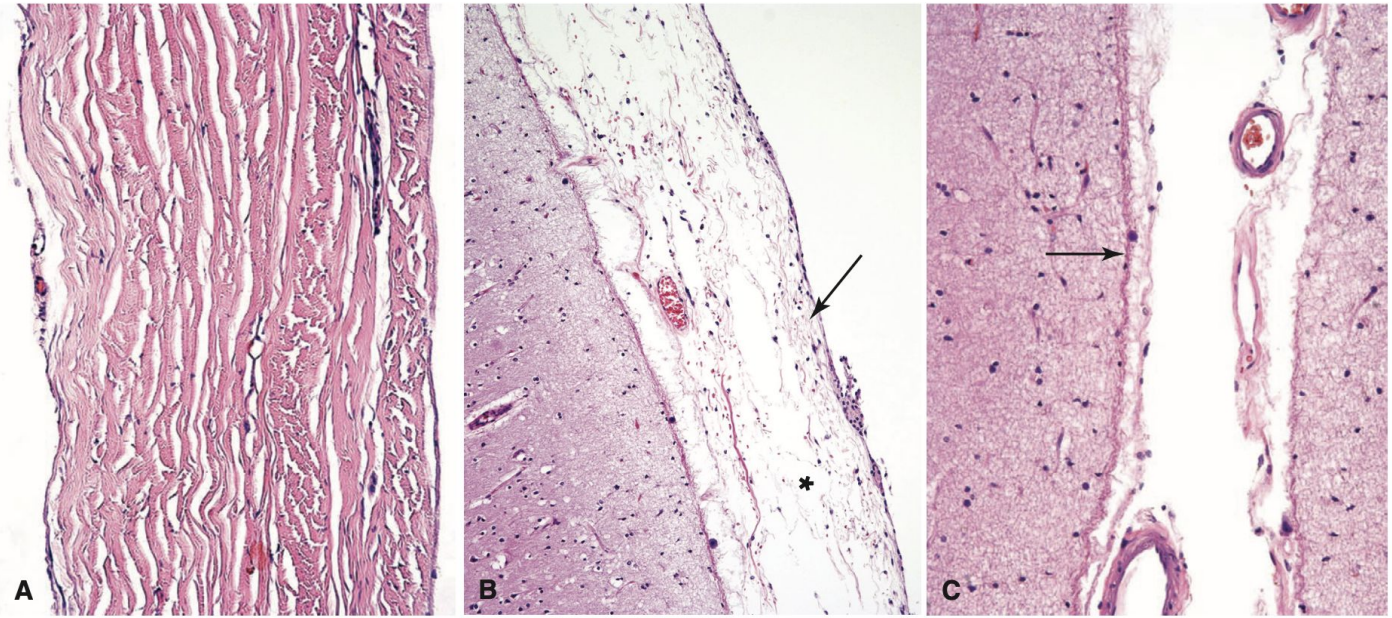
Meninges

Pachymeninges

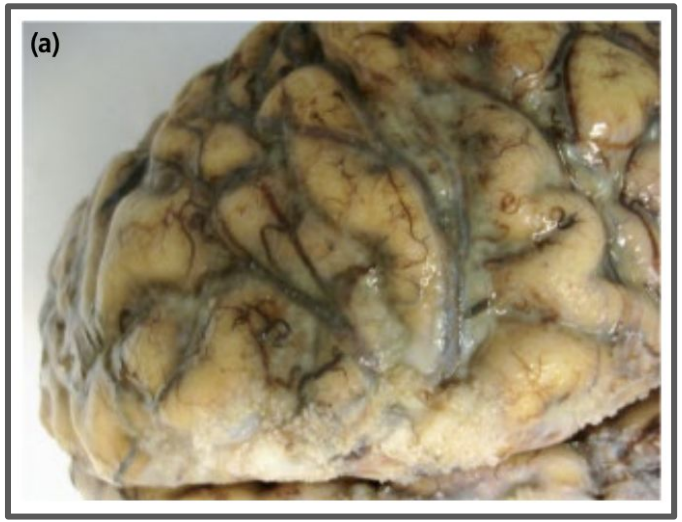
Leptomeninges



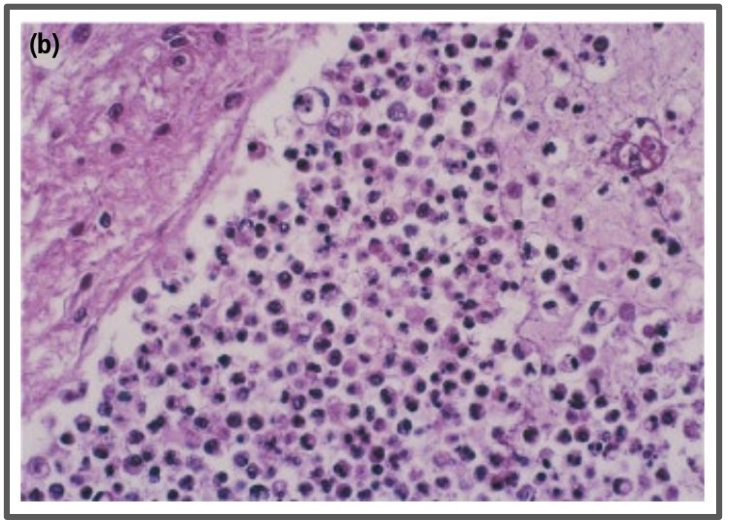
Brat D.J. Normal Brain Histopathology.Practical Surgical Neuropathology, 2016; 19-37

Meninges

Pathology : Leptomeningitis



Meningeal exudate in acute meningitis
Thin creamy lines of exudate alongside meningeal vessels

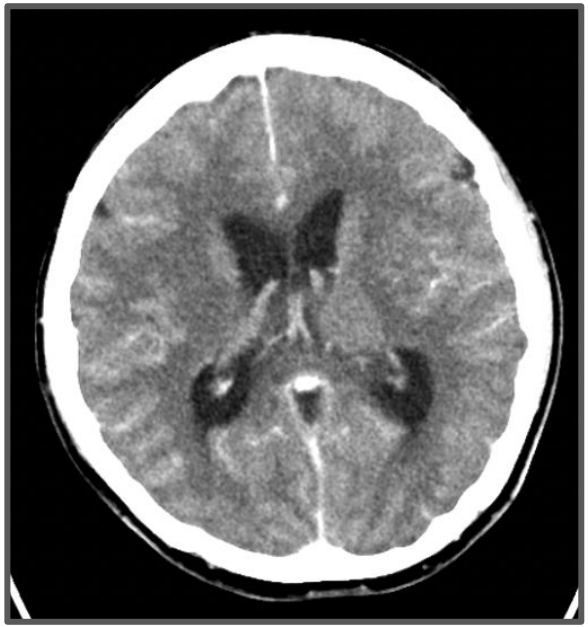


The meningeal cellular exudate is composed almost entirely of polymorphs and bacteria are both intracellular and extracellular.

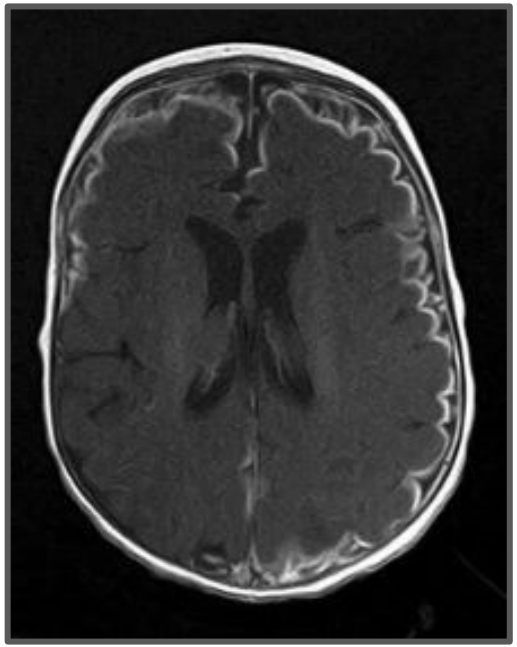
Guennec L. L., and Bourdoulous S. Pyogenic Infections of the CNS 1: Acute Bacterial Meningitis. Infections of the Central Nervous System: Pathology and Genetics. 2020; 295 – 308

Meninges

Imaging : Leptomeningitis



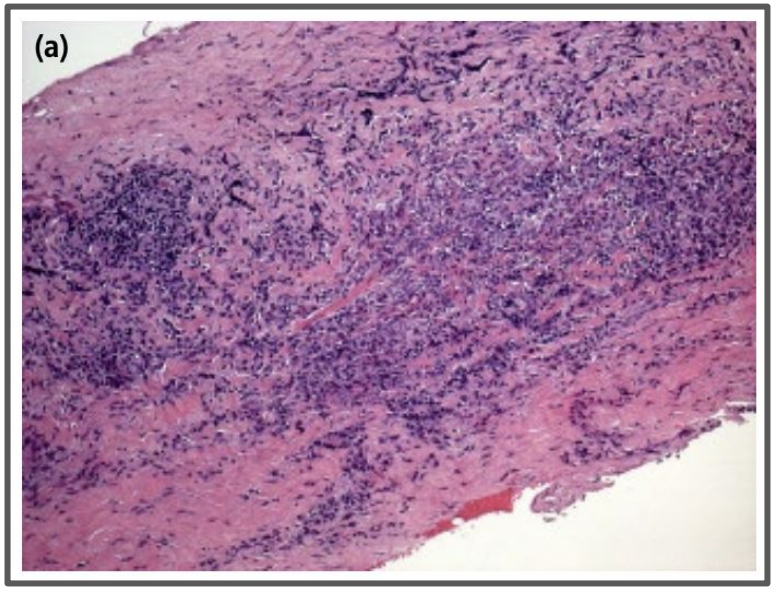
CT brain with contrast Axial view



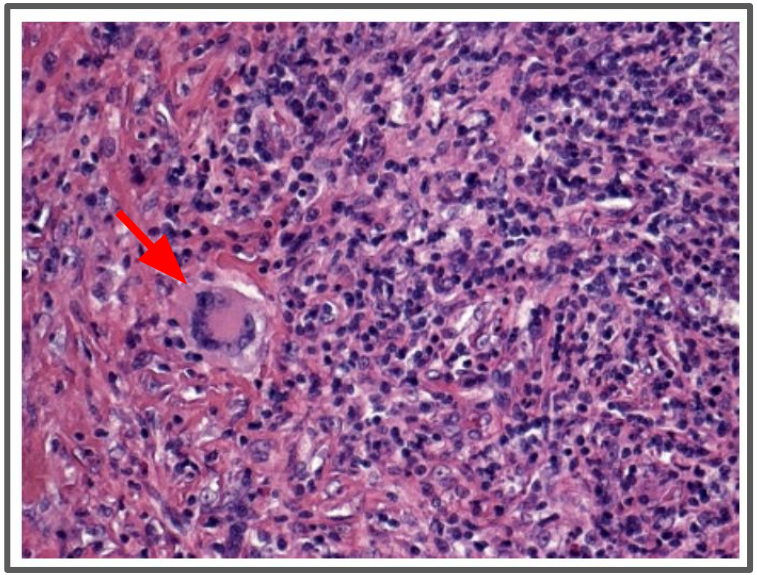
MRI brain with Gd Axial view T1

Meninges

Pathology : Pachymeningitis



Hypertrophic pachymeningitis:
characteristic fibrosis mixed with inflammatory cells.



A multinucleated giant cell is present at the border of the inflammatory infiltrate.

Meninges

Imaging Pachymeningitis

Contrast-enhanced T1-weighted MRI patterns of idiopathic hypertrophic pachymeningitis.

(A) Enhancement of cerebral falx, bilateral tentorium of cerebellum, and right parietal dura.

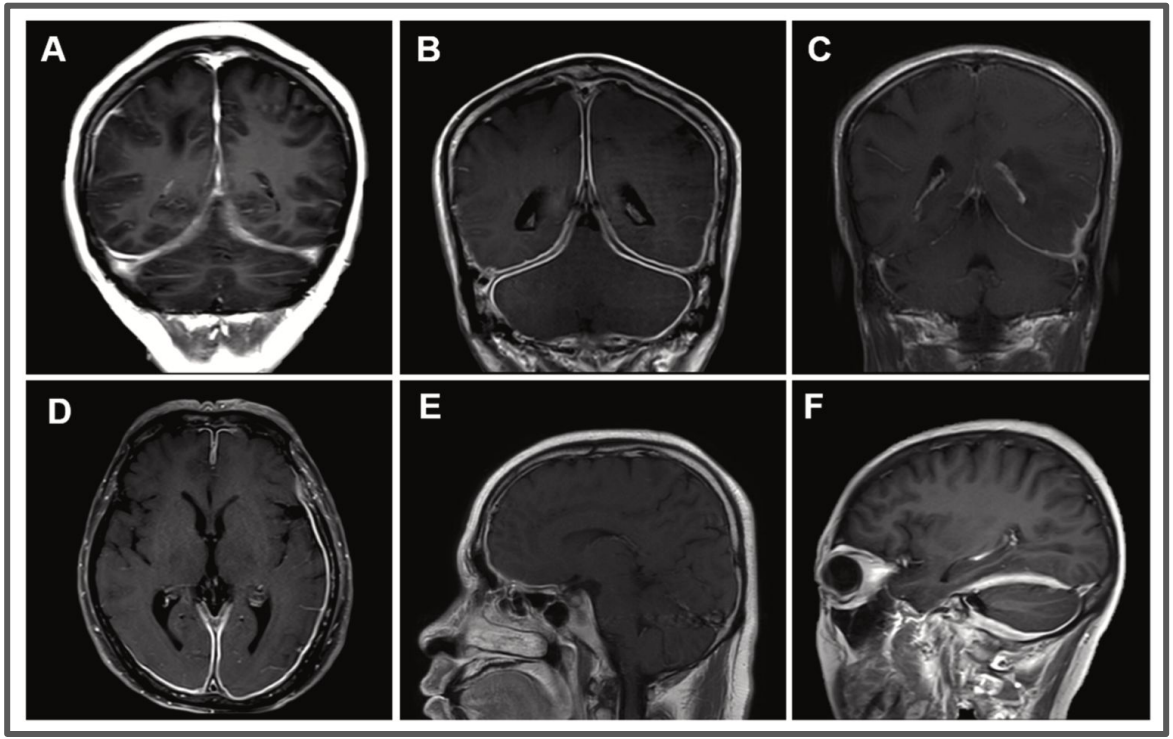
(B) Diffuse enhancement of whole dura.

(C) Enhancement of the left temporal dura and temporal lobe parenchymal involvement.

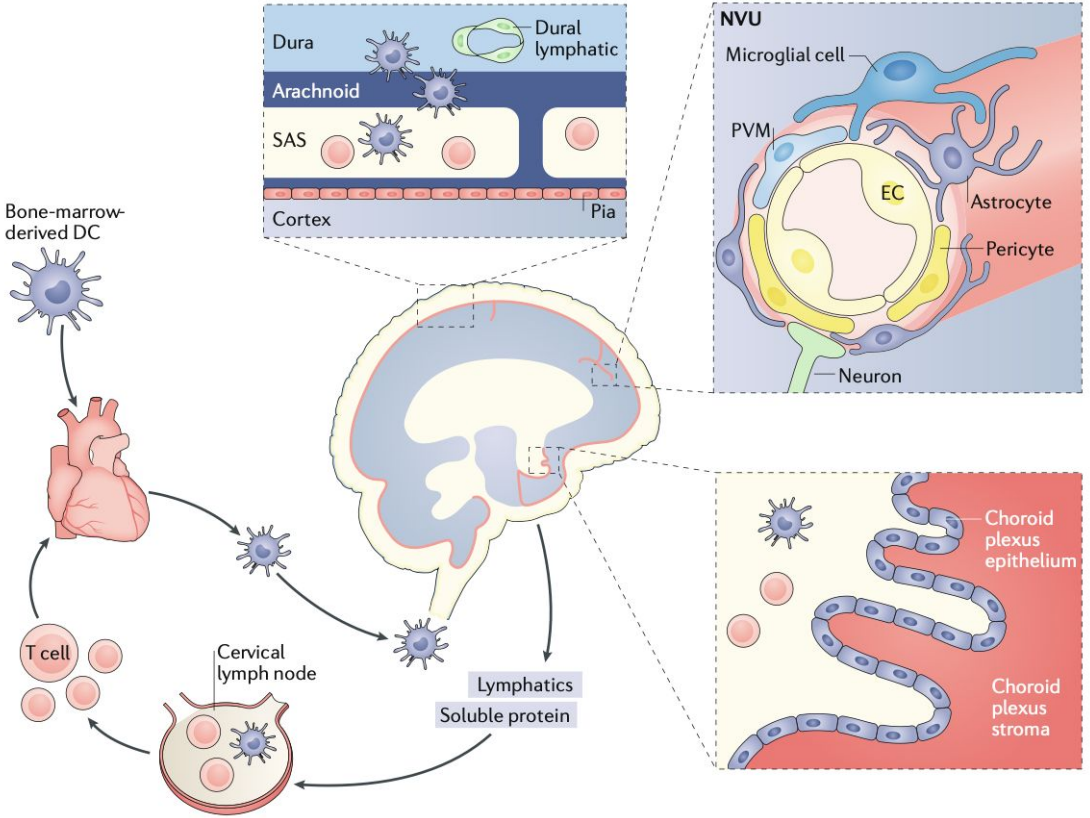
(D) Bilateral enhancement of occipital and right temporal dura.

(E) Enhancement of frontal dura.

(F) Enhancement of the tentorium cerebellum.



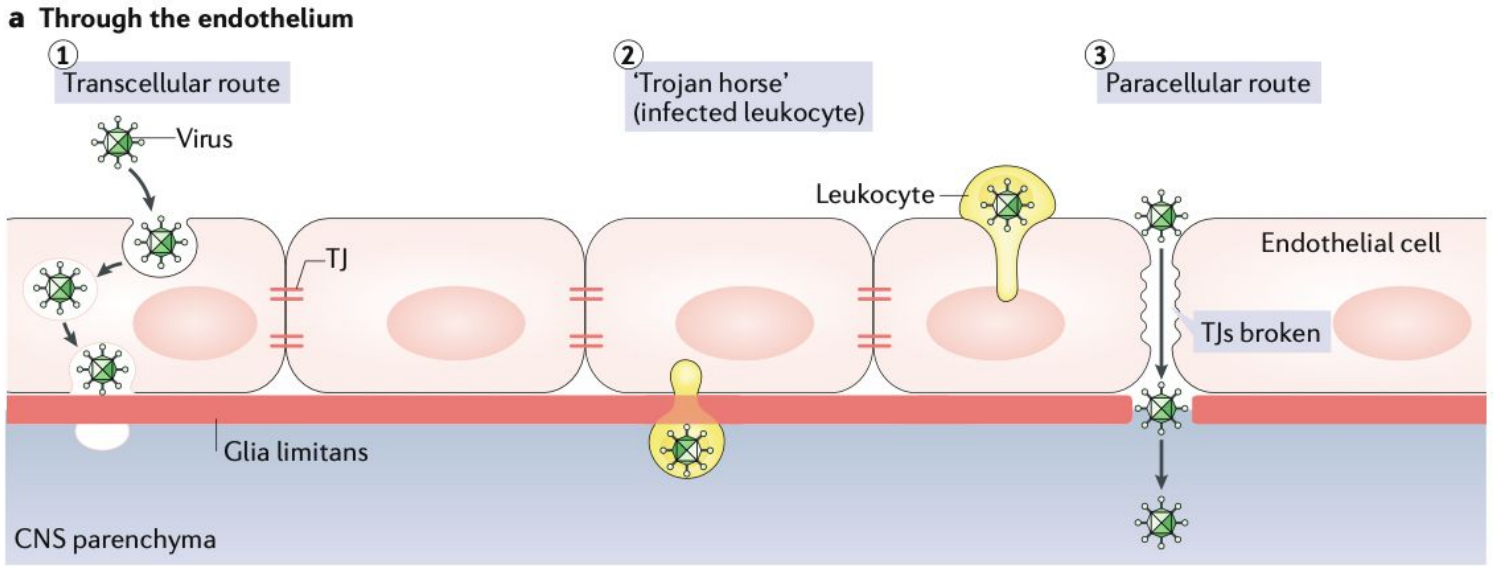
General concept of CNS infection



Forrester JV, McMenamin PG, Dando SJ. CNS infection and immune privilege. Nat Rev Neurosci. 2018;19(11):655-71.

General concept of CNS infection

CNS invasion



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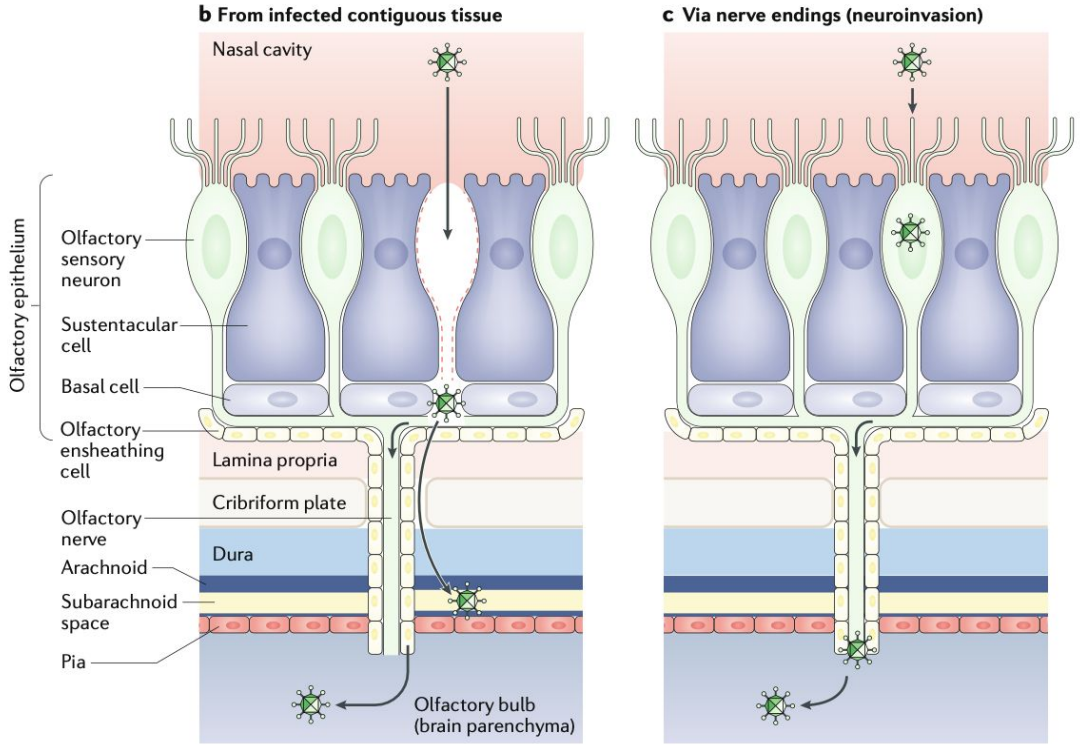
General concept of CNS infection

CNS invasion

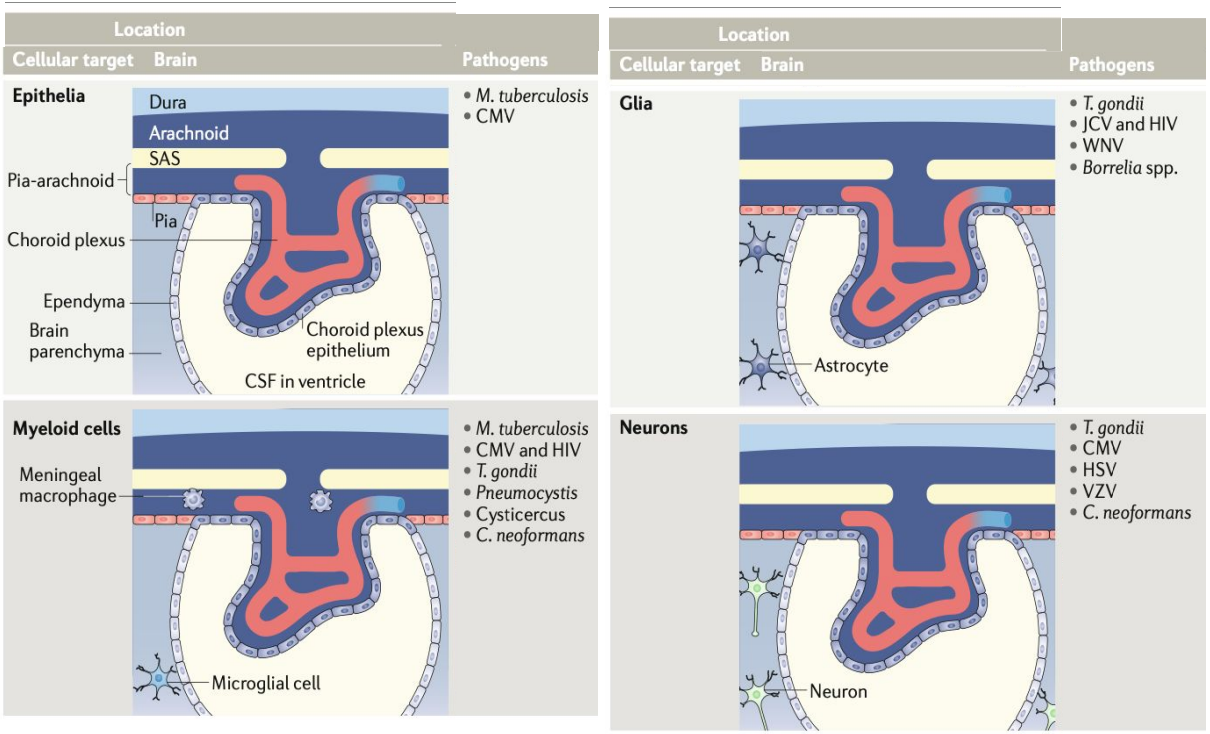


Forrester JV, McMenamin PG, Dando SJ. CNS infection and immune privilege. Nat Rev Neurosci. 2018;19(11):655-71.

General concept of CNS infection

Cellular tropism

(Neurotropism)



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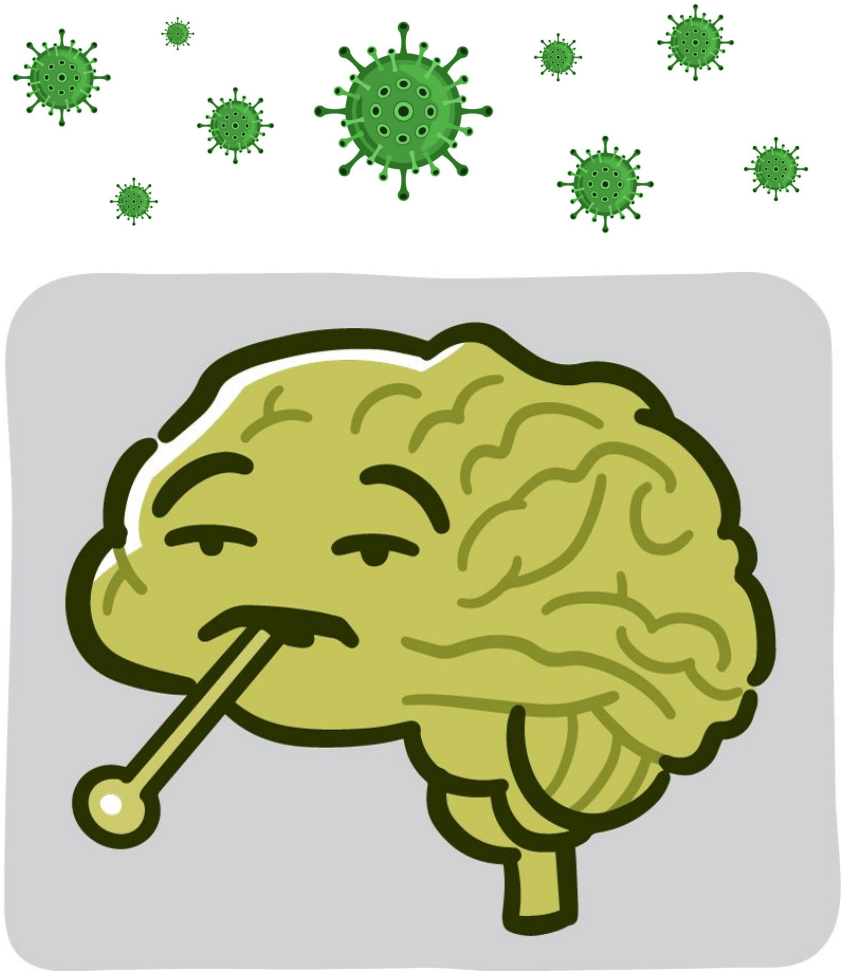


Encephalitis

Encephalitis

Definition :

Inflammation of the brain parenchyma and is caused by a wide range of infectious and autoimmune conditions.

The inflammation may be focal, multifocal, or diffuse and may also involve the meninges (meningoencephalitis) or spinal cord (encephalomyelitis)

Venkatesan A. Encephalitis and Brain Abscess. Continuum (Minneap Minn). 2021;27(4):855-86.

Encephalitis

Epidemiology

- 5 to 10 per 100,000 individuals annually
- More than half of case is Infectious cause and 20 - 30 % is immune process

Clinical manifestation

- Common clinical features of infectious encephalitis include fever and headache.
- The disturbance of brain function that is a core feature of encephalitis can manifest in a multitude of ways

Venkatesan A. Encephalitis and Brain Abscess. Continuum (Minneap Minn). 2021;27(4):855-86.

Brain region	Neuroimaging findings
Temporal lobe	
Herpes simplex virus (HSV)	Asymmetric involvement is characteristic
Varicella-zoster virus	Temporal lobe involvement can mimic HSV encephalitis
Treponema pallidum	Bilateral mesial temporal lobe involvement has been described
Human herpesvirus 6	In posttransplant limbic encephalitis, mesial temporal lobe involvement is bilateral and symmetric
Frontal lobe	
HSV	Cingulate gyrus, usually in association with temporal lobe abnormalities
Naegleria fowlerii	Necrotic, hemorrhagic lesions
Deep gray (basal ganglia/thalamus)	
West Nile virus	Imaging may be normal in early stages
Japanese encephalitis virus	Involvement of thalamus more often than the basal ganglia
Respiratory viruses	Symmetric, hemorrhagic lesions can occur in the setting of acute necrotizing encephalopathy
Rabies	Ill-defined, nonenhancing lesions
Mycobacterium tuberculosis	Involvement of basal ganglia more often than thalamus
Rocky Mountain spotted fever	"Starry sky" appearance in children, involving deep white and gray matter

Limbic system involvement

Venkatesan A. Encephalitis and Brain Abscess. Continuum (Minneap Minn).

Encephalitis

Brain region	Neuroimaging findings
Cerebellum	
Varicella-zoster virus	Brain MRI may be normal despite clear cerebellar signs on examination
West Nile virus	Usually in association with deep gray matter abnormalities
Powassan virus	Imaging abnormalities can be multifocal and variable
Mycoplasma pneumoniae	Lesions can be large with associated mass effect
Brainstem	
Enteroviruses	Brainstem involvement most commonly associated with enterovirus 71 (EV71) and enterovirus D68 (EVD68)
West Nile virus	Usually in association with deep gray matter abnormalities
Japanese encephalitis virus	Usually in association with deep gray matter abnormalities
Rabies	Ill-defined, nonenhancing lesions
Listeria monocytogenes	Multiple enhancing lesions of pons and medulla is characteristic
M. pneumoniae	Lesions can be large with associated mass effect

Venkatesan A. Encephalitis and Brain Abscess. Continuum (Minneap Minn). 2021;27(4):855-86.

Encephalitis

Herpes simplex virus

Herpes simplex virus

- HSV 1 more common for encephalitis but HSV 2 more common in meningitis

Clinical presentation

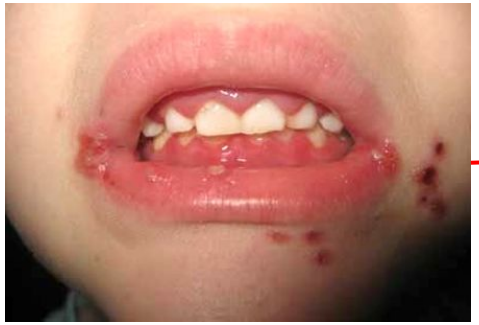
- Fever (90%–100%)
- Headache (70%–81%)
- Seizures (40%–68%)[M/C Temporal lobe semiology]
- Behavior change (41%–87%)
- Motor deficit (30%–40%)
- Altered consciousness (97%–100%)
- Disorientation (70%–76%)
- Memory disturbance (24%–45%)
- Speech disturbances (31%–59%)

Area involvement : Mesial temporal, Orbitofrontal, Insular cortex, Cingulate gyrus

Venkatesan A. Encephalitis and Brain Abscess. Continuum (Minneap Minn).

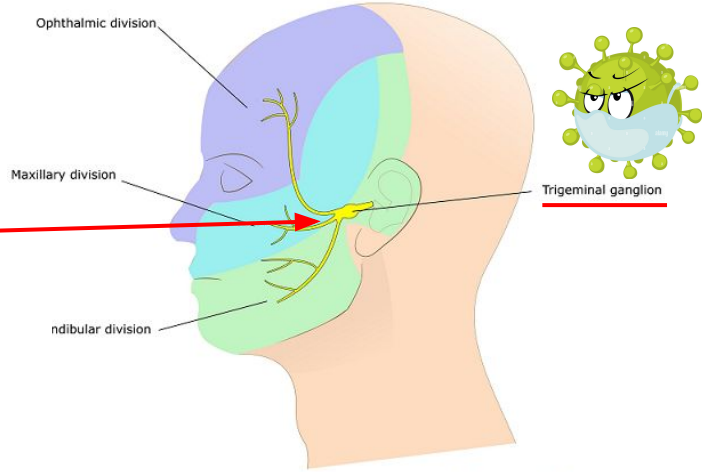
Encephalitis — Herpes simplex virus

Pathogenesis



Herpes gingivostomatitis
(Primary infection)

Retrograde Axoplasmic transport of virus



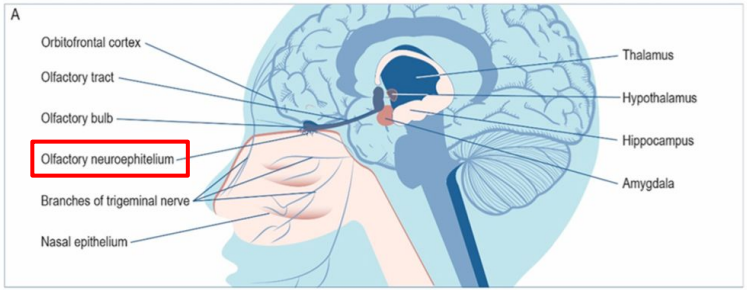
But brainstem encephalitis
VERY RARE in HSV encephalitis

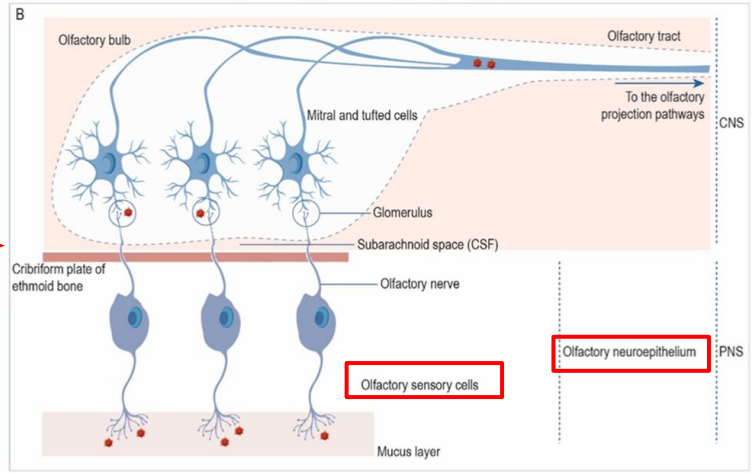
Bello-Morales R, Andreu S, Lopez-Guerrero JA. The Role of Herpes Simplex Virus Type 1 Infection in Demyelination of the Central Nervous System. Int J Mol Sci. 2020;21(14).

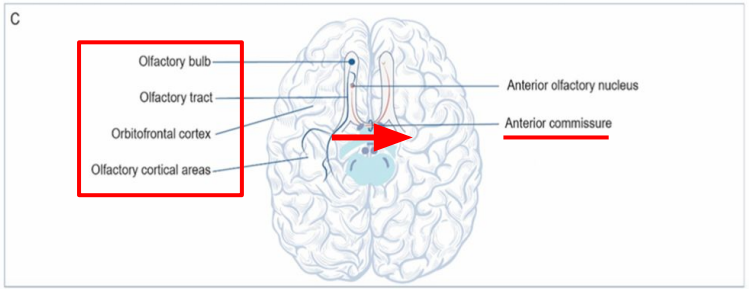
Encephalitis

Herpes simplex virus

Pathogenesis : 1.Primary infection







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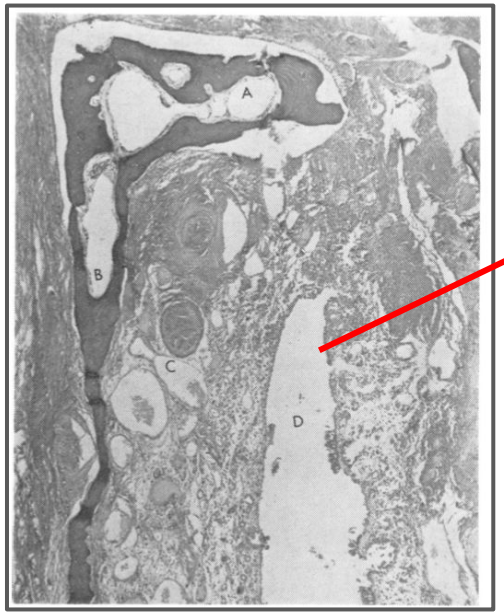
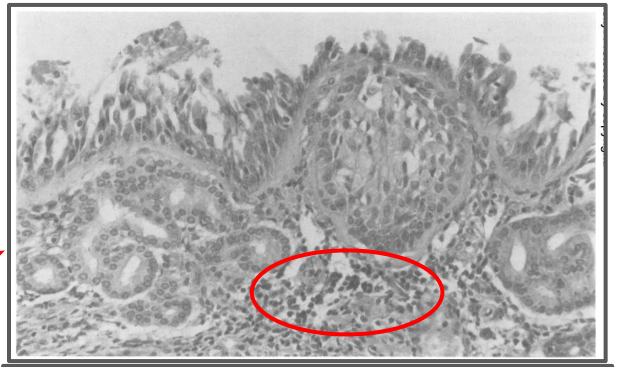
Encephalitis

Herpes simplex virus

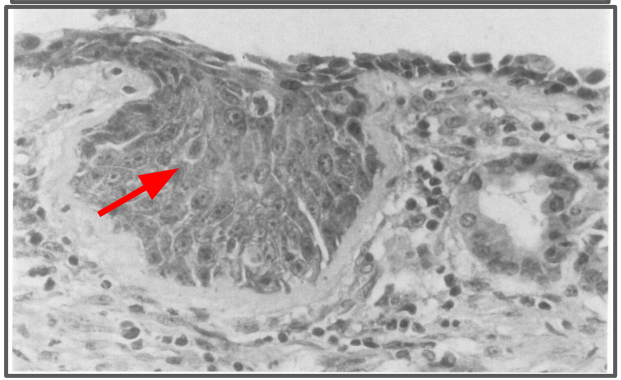
Histology : 1.Primary infection



Olfactory space



Lymphocyte and plasma cell infiltrated



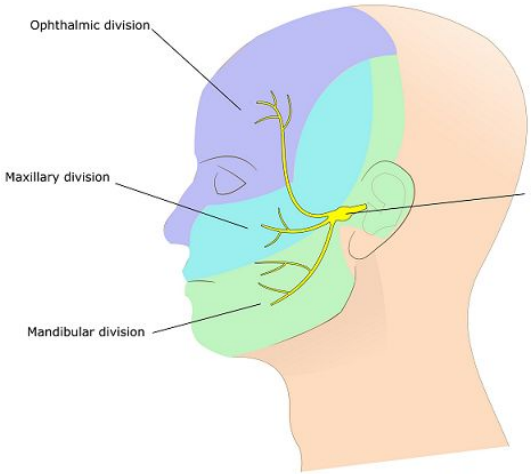
Ballooning and inclusion body present in infected cell

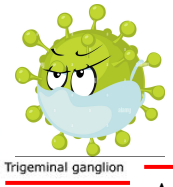
Twomey JA, Barker CM, Robinson G, Howell DA. Olfactory mucosa in herpes simplex encephalitis. J Neurol Neurosurg Psychiatry. 1979;42(11):983-7.

Encephalitis

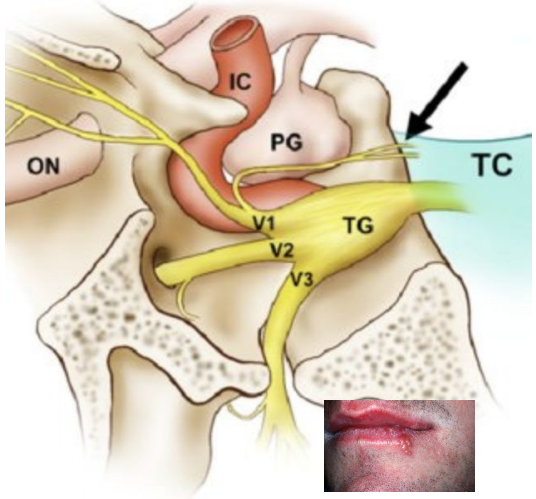
Herpes simplex virus

Pathogenesis : 2.Reactivation of latent infection





Anterograde transport



A recurrent branch of opthalmic nerve within the lateral wall of the cavernous sinus, the nervus tentorii. Fibers clearly innervate the dura of the middle and anterior fossa, form perivascular plexuses.

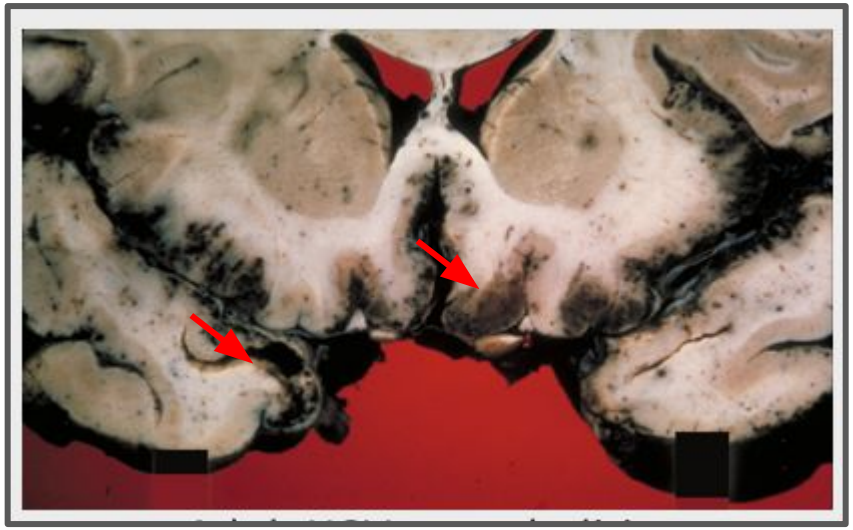
Davis LE, Johnson RT. An explanation for the localization of herpes simplex encephalitis? Ann Neurol. 1979;5(1):2-5.

Encephalitis

Herpes simplex virus

Gross pathology

Show diffuse softening and edema, accentuated by hemorrhagic necrosis of the inferior frontal and temporal lobes

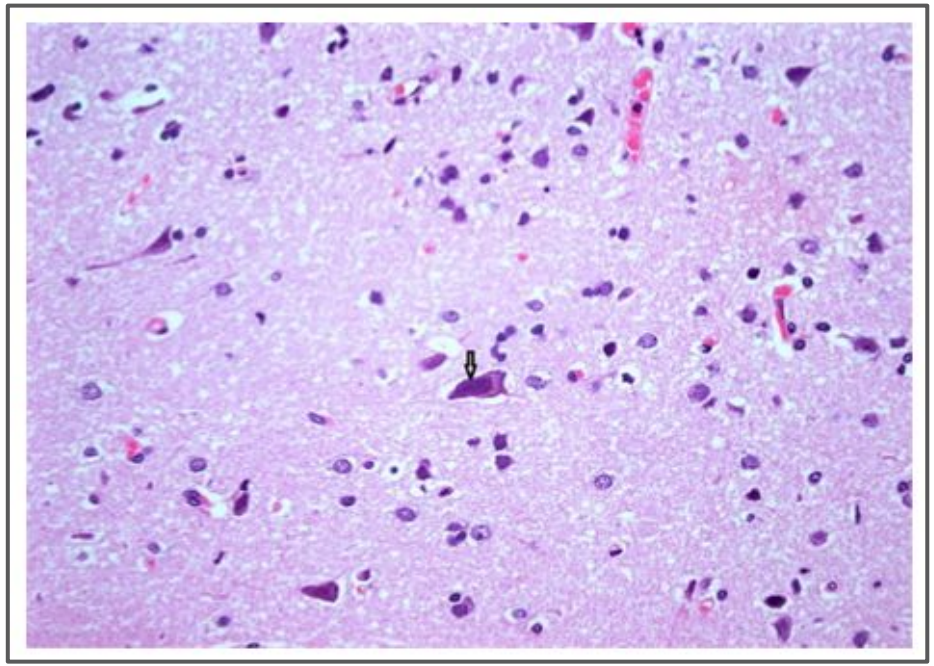


Kleinschmidt-DeMasters B. K., Keohane C. K.Herpes Simplex Virus Infections of the CNS.Infections of the Central Nervous System: Pathology and Genetics. 2020; 43-54

Encephalitis

Herpes simplex virus

Histopathology



Diffuse encephalitis findings and intranuclear inclusion bodies compatible with viral infection on histopathology

Kaya A, Kurt AF, Sili U, Kaya SY, Sahin Z, Sar M, et al. Untreated herpes simplex virus encephalitis without a fatal outcome. J Neurovirol. 2021;27(3):493-7.

Encephalitis — Herpes simplex virus

Investigation

CSF examination

- 96% to 100% of patients have a CSF pleocytosis (>5 white blood cells/mm3) with a lymphocytic predominance.[PMN predominated in early stage]
- The protein is usually elevated (mean and median, 80–85 mg/dL)
- The glucose level is normal in 95% of cases.[or mild hypoglycorrhachia]
- PCR tests for HSV exhibit sensitivity >95% and specificity >99%

Venkatesan A. Encephalitis and Brain Abscess. Continuum (Minneap Minn). 2021;27(4):855-86.

Encephalitis

Herpes simplex virus

Investigation :

Imaging

- Brain MRI typically demonstrates T2 hyperintensity and swelling of limbic structures including mesiotemporal, orbitofrontal, and insular regions, with associated restriction of diffusion

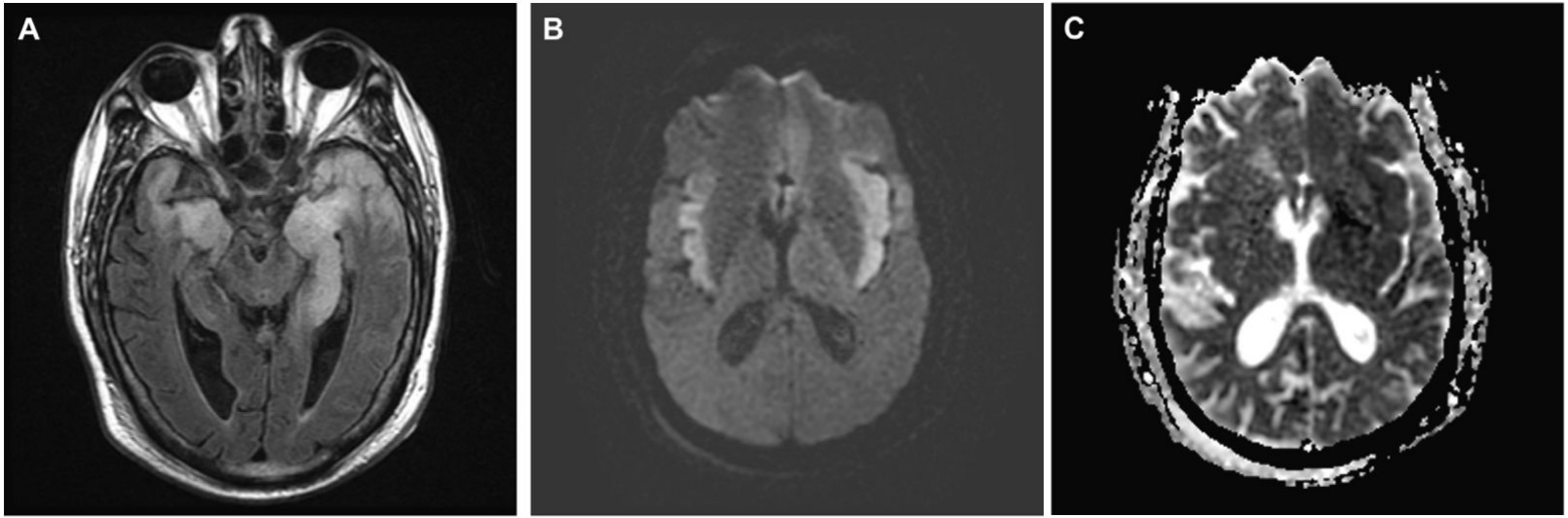
- Early in the disease course, findings are often unilateral when bilateral, **asymmetry** may help to distinguish HSV-1 encephalitis from autoimmune causes of limbic encephalitis,

Venkatesan A. Encephalitis and Brain Abscess. Continuum (Minneap Minn). 2021;27(4):855-86.

Encephalitis

Herpes simplex virus

Investigation : Imaging



(A) image demonstrates bilateral, asymmetric temporal lobe signal abnormalities. Diffusion-weighted image (B) and the corresponding ADC map (C) demonstrate areas of restricted diffusion.

Venkatesan A. Encephalitis and Brain Abscess. Continuum (Minneap Minn). 2021;27(4):855-86.

Encephalitis

Herpes simplex virus

Treatment

- IV acyclovir 10(-15) mg/kg every 8 hours is the drug of choice
- The recommended duration of acyclovir therapy is 14 to 21 days according to the IDSA guidelines

>> **Steroid**

>> there is no proven benefit of adjunctive steroid therapy

>> Maybe consider in severe case with cerebral edema to manage IICP

Beckham J. D., Tyler K. L. Encephalitis. Mandell. 2020; 1226-47

Encephalitis

Herpes simplex virus

Treatment

Prognosis Factor for HSV encephalitis

- Patient age
- Level of consciousness
- Immune suppression
- Duration of clinical encephalitis before initiation of acyclovir therapy

>> IDSA guideline advise that acyclovir should be initiated in "all patients" with suspected encephalitis

Beckham J. D., Tyler K. L. Encephalitis. Mandell. 2020; 1226-47

Encephalitis

Varicella zoster virus

Varicella zoster virus(VZV)

- Primary VZV infection (chickenpox) occurs mainly in children 1 to 9 years old, and seroprevalence by adult life is greater than 95%.
- After primary infection, the virus establishes latency in dorsal root ganglia

VZV CNS infection can occur during

- Primary infection
- After viral reactivation from latency.
  - >> ⅓ of the case develop CNS infection without rash
  - >> onset few week to 4 months after reactivation

Beckham J. D., Tyler K. L. Encephalitis. Mandell. 2020; 1226-47

Encephalitis

Varicella zoster virus

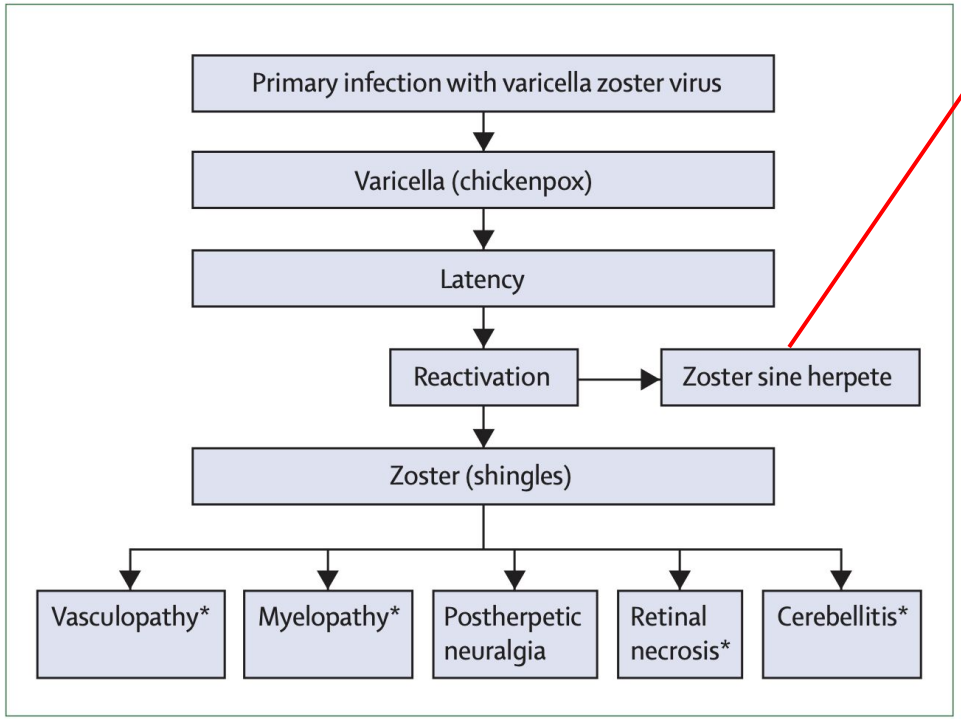


Figure 1: **Neurological disease caused by reactivation of varicella zoster virus**
*Can occur after varicella and can also occur without a rash.

<u>Zoster sine herpete :</u>
Infection and reactivation of the varicella-zoster virus (VZV) in the cranial nerve, spinal nerve, viscera, or autonomic nerve.

Gilden D, Cohrs RJ, Mahalingam R, et al. Varicella zoster virus vasculopathies: diverse clinical manifestations, laboratory features, pathogenesis, and treatment. Lancet Neurol 2009;8(8):731–40.

Encephalitis

Varicella zoster virus

Pathogenesis :

1.Primary infection >> Cerebellitis

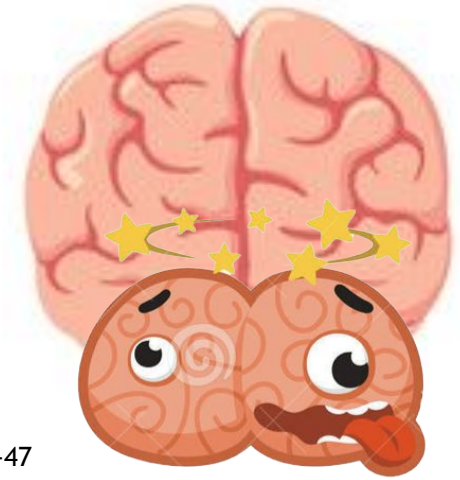
>> Unclear, Suspected due to

direct viral infection in the CNS

or postinfectious immune-mediated state.

>> The clinical presentation occurring 1 to 3 weeks after onset of chickenpox.

> in children



Beckham J. D., Tyler K. L. Encephalitis. Mandell. 2020; 1226-47

Encephalitis

Varicella zoster virus

Table 1 Comparison of the cases in literature reporting varicella zoster cerebellitis in adults with our current case

Case	A	B	C	D	E	F	G
Year	2022	2019	2018	2015	2012	2006	2006
Age	70s	50s	80s	80s	70s	40s	60s
Gender	Female	Male	Male	Male	Female	Female	Male
Risk factors	Elderly	None	Elderly	Elderly	Elderly	None	Elderly
Rash	No	No	No	No	No	No	No
Radiology	CT negative MRI negative	CT positive MRI negative	MRI SPECT positive	CT negative MRI negative	MRI negative	CT negative MRI negative DWI negative	MRI negative
1st CSF	458 cells/μL	104 cells/μL VZV PCR positive	138 cells/μL VZV IgM and IgG positive VZV DNA PCR positive	13 wbc/mm^3	119 cells/μL VZV IgM and IgG positive VZV DNA PCR positive	870 cells/mm^3	66 cells/μL VZV DNA PCR positive

Case A represents our case where CT and MRI investigations did not indicate any abnormalities. Case B summarises the findings from Cross *et al*.[13] CT showed mild ventriculomegaly with features of normal pressure hydrocephalus while MRI with or without gadolinium did not show enhancement of cerebellum or pons. Case C summarises the findings from Hirofumi and Ohi.[12] In this case, SPECT on days 28 and 68 indicated hyperperfusion of the cerebellum. Case D summarises the findings from Shilo *et al* in which their case had a normal CT and MRI.[11] Case E summarises the findings from Suzuki *et al*.[10] MRI before and after gadolinium did not show any abnormalities. In this case, CT, MRI with and without gadolinium and T1, T2 DWIs did not show any abnormalities. Case F summarises the findings from Moses *et al*.[8] Case G summarises the findings from Ratzka *et al*.[9] The MRI of the brain of Case G did not show any abnormalities.

CSF, cerebrospinal fluid; DWI, diffusion-weighted image; SPECT, single-photon emission CT; VZV, varicella zoster virus.

Enwo OO, Ibrahim D, Boughton M, Coyle-Gilchrist I. Varicella zoster virus cerebellitis without skin manifestations in an immunocompetent adult. BMJ Case Rep. 2023;16(1).

Encephalitis | Varicella zoster virus

Pathogenesis :

2.Reactivation of latent infection

>> Modern studies suggest that most cases of VZV “encephalitis” are actually caused by VZV CNS vasculopathy

Large vessels (granulomatous arteritis) in immunocompetent patients
Small vessels in immunocompromised patients

>> Onset few week to 4 months after reactivation

Beckham J. D., Tyler K. L. Encephalitis. Mandell. 2020; 1226-47

Encephalitis

Varicella zoster virus

Pathogenesis :

2.Reactivation of latent infection

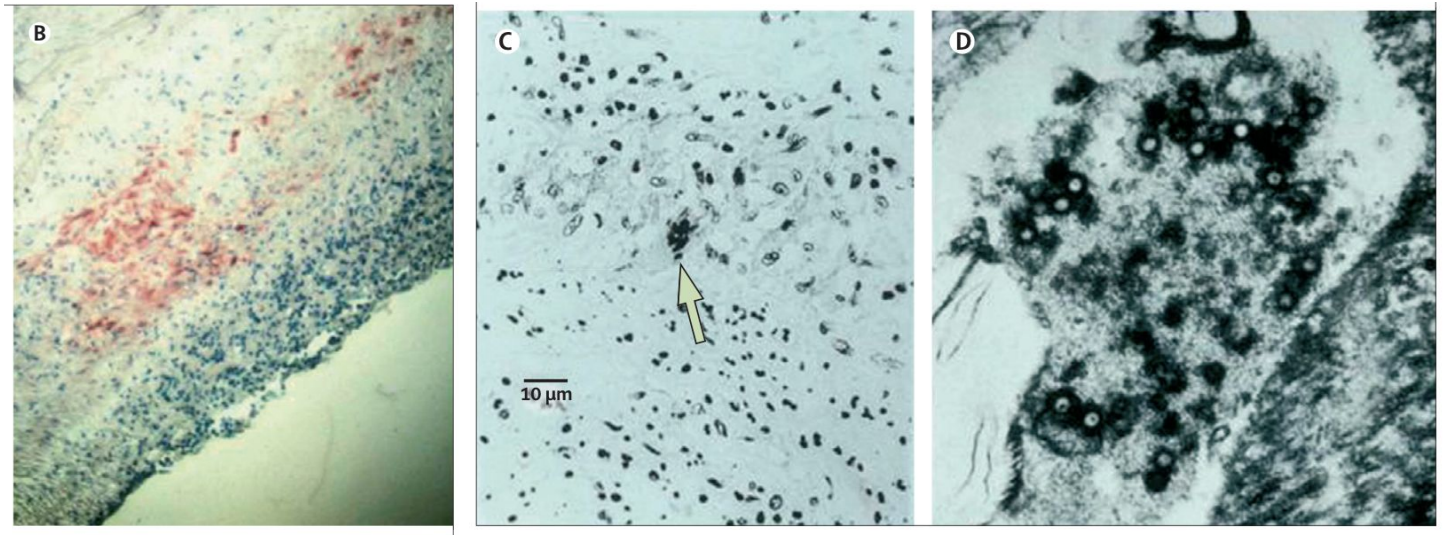
>> Afferent sensory fibres from trigeminal ganglion, corresponding to the ophthalmic division of the trigeminal nerve, innervate to ipsilateral middle cerebral artery providing an anatomical pathway for the transaxonal spread (Retrograde axonal transport) of virus.

Gilden D, Cohrs RJ, Mahalingam R, Nagel MA. Varicella zoster virus vasculopathies: diverse clinical manifestations, laboratory features, pathogenesis, and treatment. Lancet Neurol. 2009;8(8):731-40.

Encephalitis

Varicella zoster virus

Histology



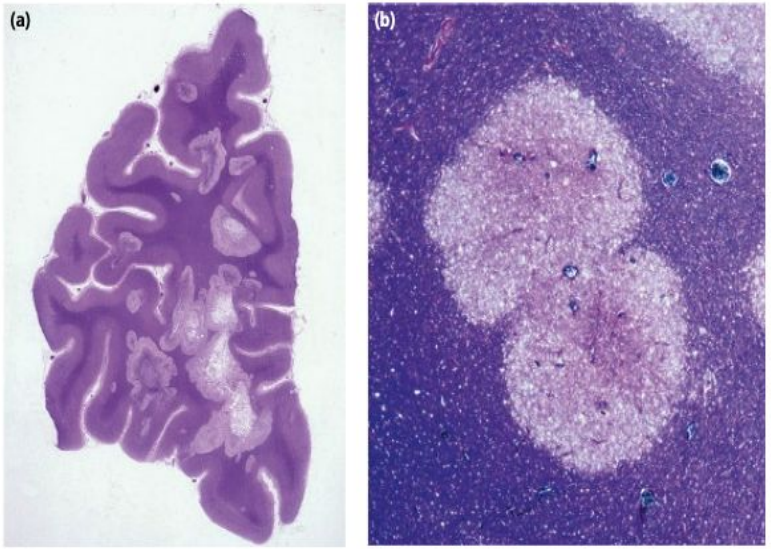
(B) VZV antigen (red) in the media of a cerebral artery.
(C) Cerebral artery with multinucleated giant cells (arrow).
(D) Multiple herpes virions within a cerebral artery via EM.

Gilden D, Cohrs RJ, Mahalingam R, Nagel MA. Varicella zoster virus vasculopathies: diverse clinical manifestations, laboratory features, pathogenesis, and treatment. Lancet Neurol. 2009;8(8):731-40.

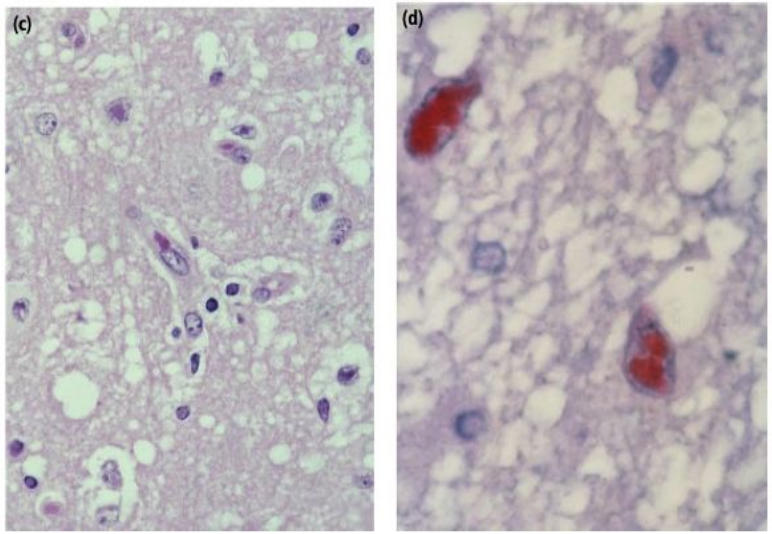
Encephalitis

Varicella zoster virus

Histology



(a,b) Multifocal leukoencephalitis with Multiple necrotic foci in GW junction



(c,d) In edematous zone, numerous cells (i.e. neurons, glia, and endothelial cells) are positively immunostained for VZV.

Keohane C. K., Gray F. Varicella-Zoster Virus and Epstein-Barr Virus Infections of the CNS. Infections of the Central Nervous System: Pathology and Genetics. 2020; 55-64

Encephalitis

Varicella zoster virus

Investigation : Imaging

Large vessel VZV vasculopathy

>> MRI findings are abnormal in 97%, with multifocal hyperintense lesions on T2-weighted FLAIR images Lesions are typically located in the white matter or at the gray-white matter junction. >> **Multifocal leukoencephalitis**

>> Angiogram : focal narrowing of vessel

Small vessel VZV vasculopathy

- Multifocal infarction

Venkatesan A. Encephalitis and Brain Abscess. Continuum (Minneap Minn). 2021;27(4):855-86.

Encephalitis

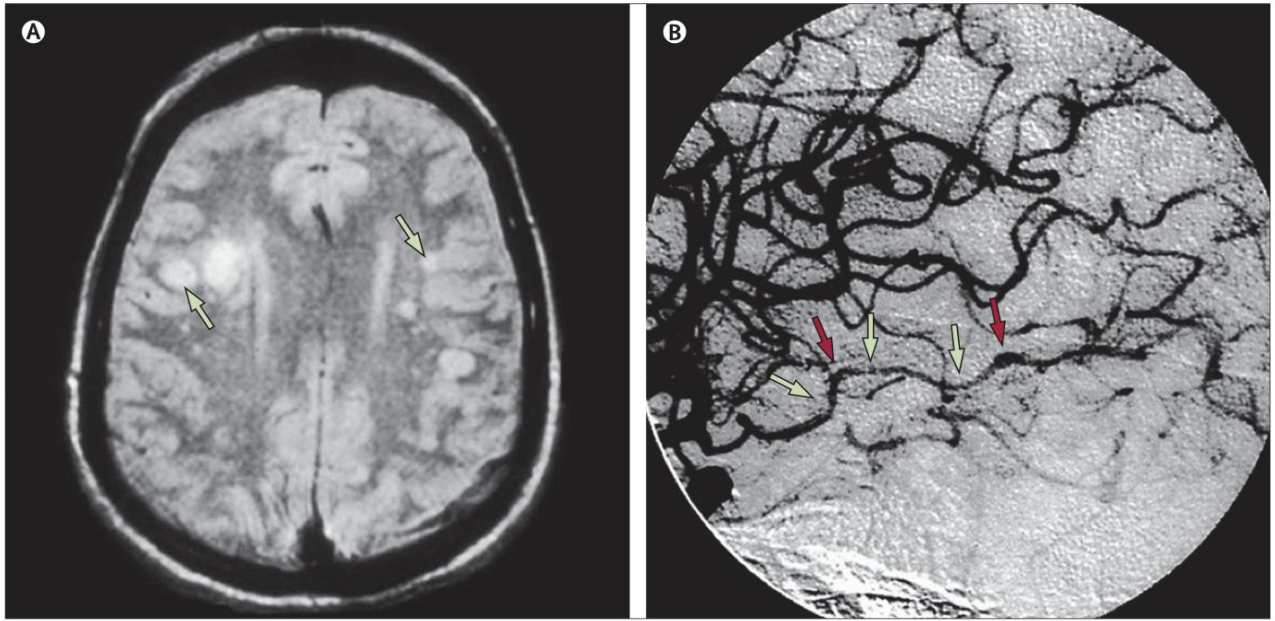
Varicella zoster virus

Investigation :

Imaging

A: Multiple areas of infarction, particularly involving the white matter. Arrows point to lesions at the grey–white matter junctions.

B : Focal areas of stenosis (green arrows) and poststenotic dilatation (red arrows)



Gilden D, Cohrs RJ, Mahalingam R, Nagel MA. Varicella zoster virus vasculopathies: diverse clinical manifestations, laboratory features, pathogenesis, and treatment. Lancet Neurol. 2009;8(8):731-40.

Encephalitis — Varicella zoster virus

Investigation

CSF examination

- Typical CSF findings include lymphocytic pleocytosis (67%), elevated protein level, and normal glucose level.
- Small vessel VZV vasculopathy(Mostly in immunocompromised patient)
  > mild pleocytosis and a normal-to-mild elevation in CSF protein.
- Sensitivity of PCR for VZV is lower than that of HSV, thus in some cases, the diagnosis is made by detection of anti-VZV antibodies(IgG) in the CSF.

Venkatesan A. Encephalitis and Brain Abscess. Continuum (Minneap Minn). 2021;27(4):855-86.

Encephalitis Varicella zoster virus

Treatment

IDSA Suggest

- IV acyclovir 10 - 15 mg/kg IV q 8 hr duration 10 - 14 days
- The adjunctive corticosteroids can be considered (category III-B)
  >> Equivalent dose of prednisolone 60 – 80 mg/day
- Ganciclovir can be considered an alternative

Tunkel AR, Glaser CA, Bloch KC, et al. The management of encephalitis: clinical practice guidelines by the infectious diseases society of America. *Clin Infect Dis*. 2008;47:303–327.

Encephalitis

Cytomegalovirus(CMV)

Cytomegalovirus(CMV)

- Occur almost exclusively in patients with a severely suppressed immune system, most commonly with CD4+ cell <50 cells/mm3 in HIV patient.

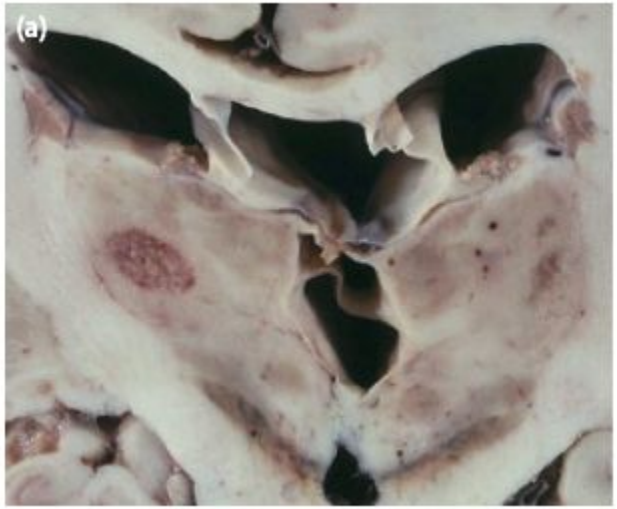
- Latent infection in myeloid cell(Meningeal macrophage,Microglia)

Bowen LN, Smith B, Reich D, Quezado M, Nath A. HIV-associated opportunistic CNS infections: pathophysiology, diagnosis and treatment. Nat Rev Neurol. 2016;12(11):662-74.

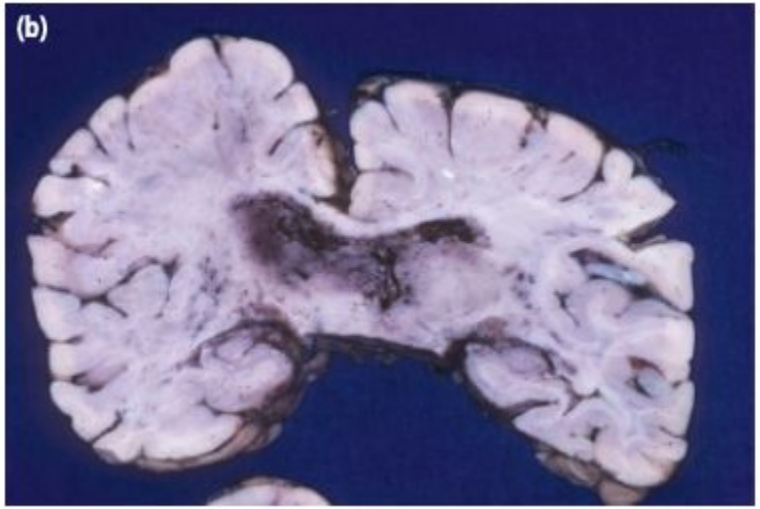
Encephalitis

Cytomegalovirus(CMV)

Gross pathology



(a): Focal parenchymal necrosis



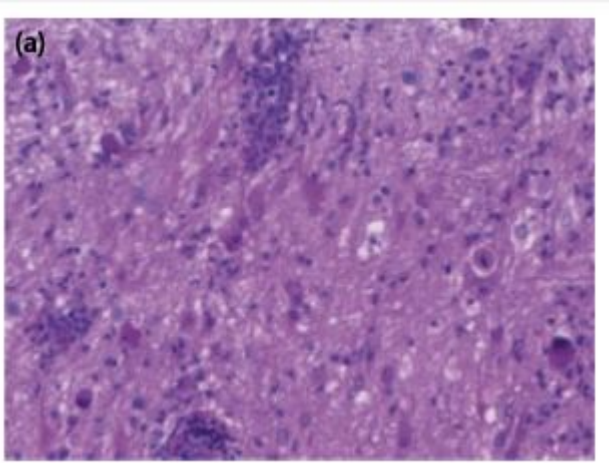
(b): Ventriculoencephalitis: the ventricular wall and the thalami are necrotic and hemorrhagic.

Biassette H.A., Teissier N.Cytomegalovirus Infections of the CNS.Infections of the Central Nervous System: Pathology and Genetics. 2020; 65-76

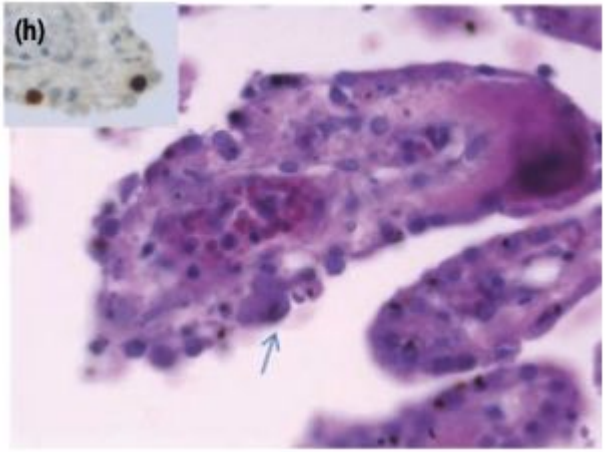
Encephalitis

Cytomegalovirus(CMV)

Histopathology



(a) Dispersed cytomegalic cells, microglial nodules (MGN), and lymphocytes.



(h) Cytomegalic cell in the epithelial lining of the choroid plexus

Biassette H.A., Teissier N.Cytomegalovirus Infections of the CNS.Infections of the Central Nervous System: Pathology and Genetics. 2020; 65-76

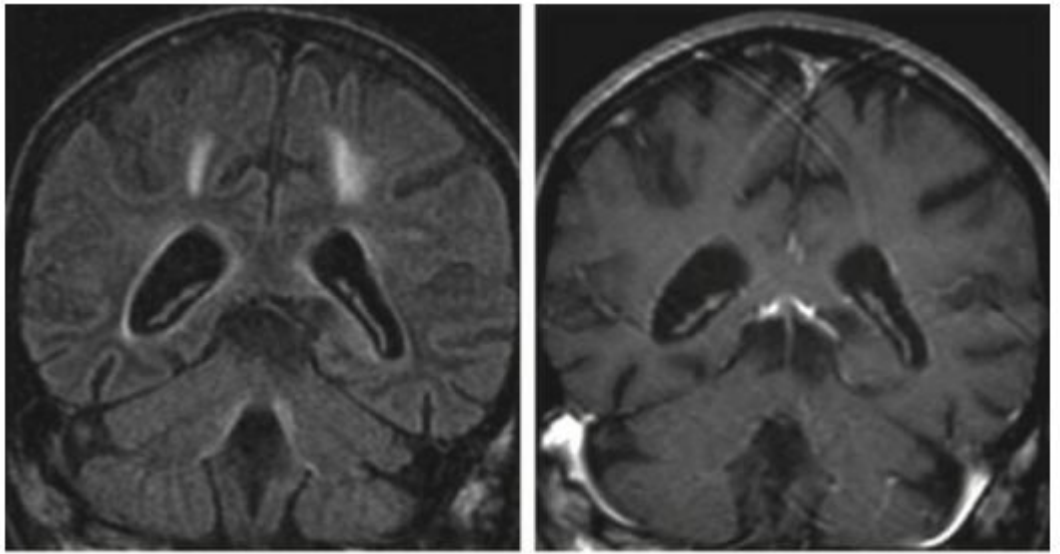
Encephalitis

Cytomegalovirus(CMV)

Imaging

(a) Coronal T2-weighted FLAIR image demonstrates circumferential hyperintensity surrounding the lateral and fourth ventricles.

(b) Coronal post-contrast T1-weighted image reveals thin, linear periventricular enhancement.



Biassette H.A., Teissier N.Cytomegalovirus Infections of the CNS.Infections of the Central Nervous System: Pathology and Genetics. 2020; 65-76

Encephalitis

Cytomegalovirus(CMV)

Treatment

Recommended initial treatment for CMV neuroinvasive disease includes the combination of

- Ganciclovir (5 mg/kg IV every 12 hours)

and Foscarnet (60 mg/kg IV every 8 hours or 90 mg/kg IV every 12 hours)

Duration 14-21 days then consider oral antiviral medication for secondary prophylaxis

Beckham J. D., Tyler K. L. Encephalitis. Mandell. 2020; 1226-47

Encephalitis

Listeria monocytogenes

Listeria monocytogenes

- Gram positive bacilli(Intracellular/Extracellular)
- Risk factor : Neonate, Pregnant, Elderly(esp > 60 years old)
- Mortality rate of 15% to 29%
- Contaminate with raw vegetables, milk, cheese, and processed meats

Rhombencephalitis

Karlsson WK, Harboe ZB, Roed C, Monrad JB, Lindelof M, Larsen VA, et al. Early trigeminal nerve involvement in Listeria monocytogenes rhombencephalitis: case series and systematic review. J Neurol. 2017;264(9):1875-84.

Encephalitis — Listeria monocytogenes

Pathogenesis

J Neurol (2017) 264:1875–1884
DOI 10.1007/s00415-017-8572-2

ORIGINAL COMMUNICATION

Early trigeminal nerve involvement in *Listeria monocytogenes* rhombencephalitis: case series and systematic review

William K. Karlsson[1] · Zitta Barrella Harboe[2] · Casper Roed[2] · Jeppe B. Monrad[1] · Mette Lindelof[1] · Vibeke Andrée Larsen[3] · Daniel Kondziella[4]

Karlsson WK, Harboe ZB, Roed C, Monrad JB, Lindelof M, Larsen VA, et al. Early trigeminal nerve involvement in Listeria monocytogenes rhombencephalitis: case series and systematic review. J Neurol. 2017;264(9):1875-84.

Encephalitis Listeria monocytogenes

Pathogenesis

1. Axonal spreading through cranial nerves
2. Hematogenous invasion of the brainstem

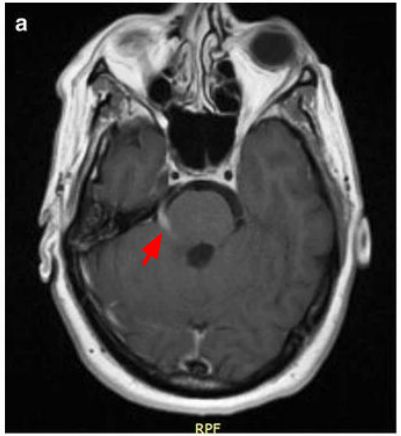
Karlsson WK, Harboe ZB, Roed C, Monrad JB, Lindelof M, Larsen VA, et al. Early trigeminal nerve involvement in Listeria monocytogenes rhombencephalitis: case series and systematic review. J Neurol. 2017;264(9):1875-84.

Encephalitis Listeria monocytogenes

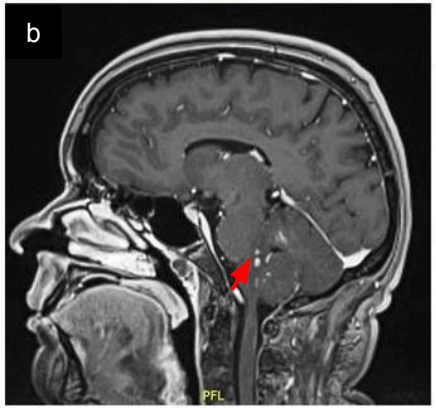
Pathogenesis 1.Axonal spreading through cranial nerves

- Cranial nerves VII, V, IX, and X, respectively

For example case



A : Early involvement of the trigeminal nerve root



B : Selective Gd enhanced in sensory trigeminal tract

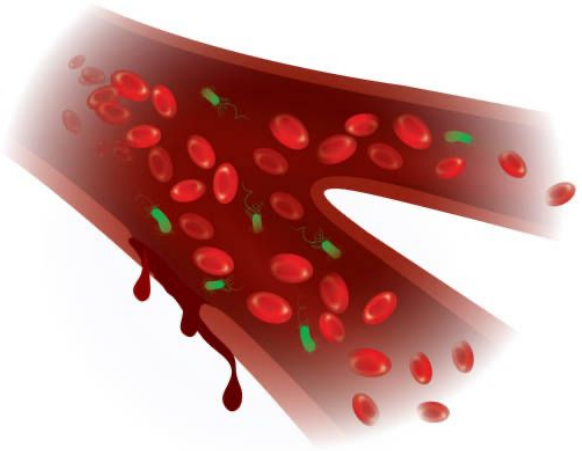
Karlsson WK, Harboe ZB, Roed C, Monrad JB, Lindelof M, Larsen VA, et al. Early trigeminal nerve involvement in Listeria monocytogenes rhombencephalitis: case series and systematic review. J Neurol. 2017;264(9):1875-84.

Encephalitis Listeria monocytogenes

Pathogenesis

2.Hematogenous invasion of the brainstem

- blood cultures were positive in 61% - 63 %



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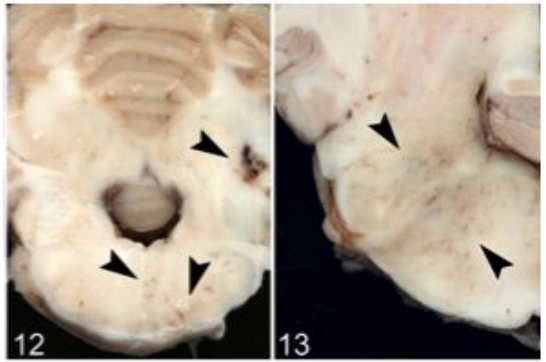
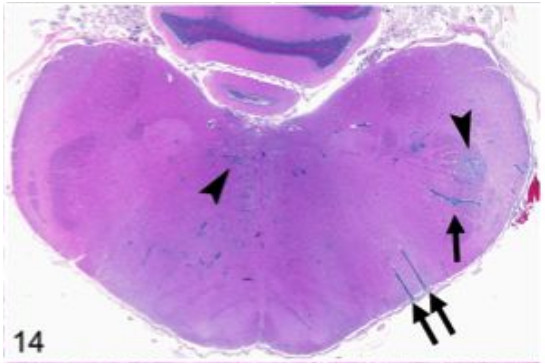
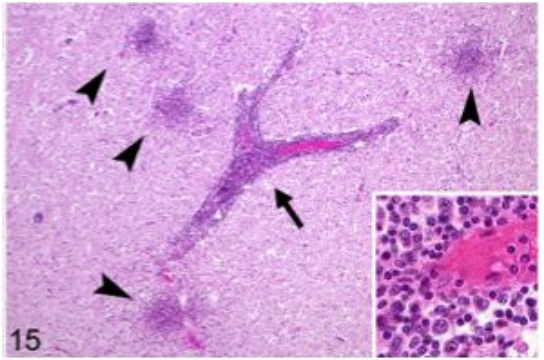
Encephalitis — Listeria monocytogenes

Pathology





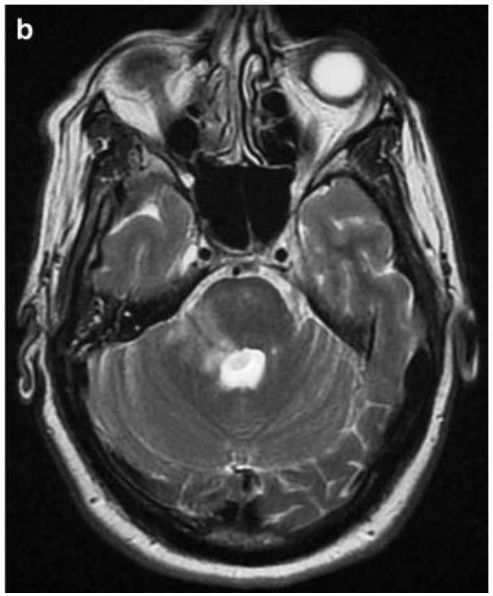


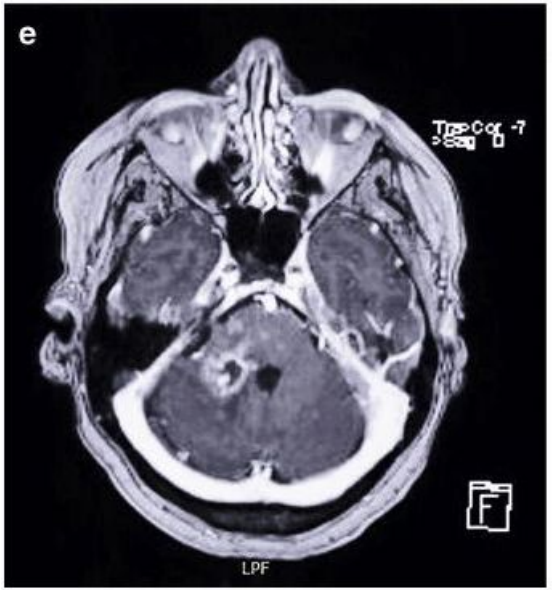
Figures 12–13.Sheep. There are multifocal areas of hemorrhage and malacia (arrowheads).
Figure 14. Sheep. Multifocal linear, deeply basophilic lesions corresponding to perivascular cuffs (arrows) and irregular, variably basophilic lesions corresponding to microabscesses (arrowheads) are present in the neuroparenchyma. HE.
Figure 15. Cow. Cardinal lesions of rhombencephalitis: microabscesses, recognizable as scattered foci of phagocytes infiltrating the neuroparenchyma (arrowheads), and a perivascular cuff (arrow), predominantly consisting of mononuclear cells accumulating in the perivascular space

Karlsson WK, Harboe ZB, Roed C, Monrad JB, Lindelof M, Larsen VA, et al. Early trigeminal nerve involvement in Listeria monocytogenes rhombencephalitis: case series and systematic review. J Neurol. 2017;264(9):1875-84.

Encephalitis Listeria monocytogenes

Imaging





Karlsson WK, Harboe ZB, Roed C, Monrad JB, Lindelof M, Larsen VA, et al. Early trigeminal nerve involvement in Listeria monocytogenes rhombencephalitis: case series and systematic review. J Neurol. 2017;264(9):1875-84.

Encephalitis Listeria monocytogenes

Clinical feature

- The majority of patients are immunocompetent (69.8%)
- Mortality is high (32.2%)
- Blood culture positive (61-63%)
- Fever at the onset (82.7%)
- Prodromal symptoms before the first neurological deficits occur (74%)
- Most common neurological symptom : Diplopia (61.8%)
- Meningeal symptoms (44.3%)

Karlsson WK, Harboe ZB, Roed C, Monrad JB, Lindelof M, Larsen VA, et al. Early trigeminal nerve involvement in Listeria monocytogenes rhombencephalitis: case series and systematic review. J Neurol. 2017;264(9):1875-84.

Encephalitis

Listeria monocytogenes

Duration : At least 21 days

Treatment specific for *L.monocytogenes*

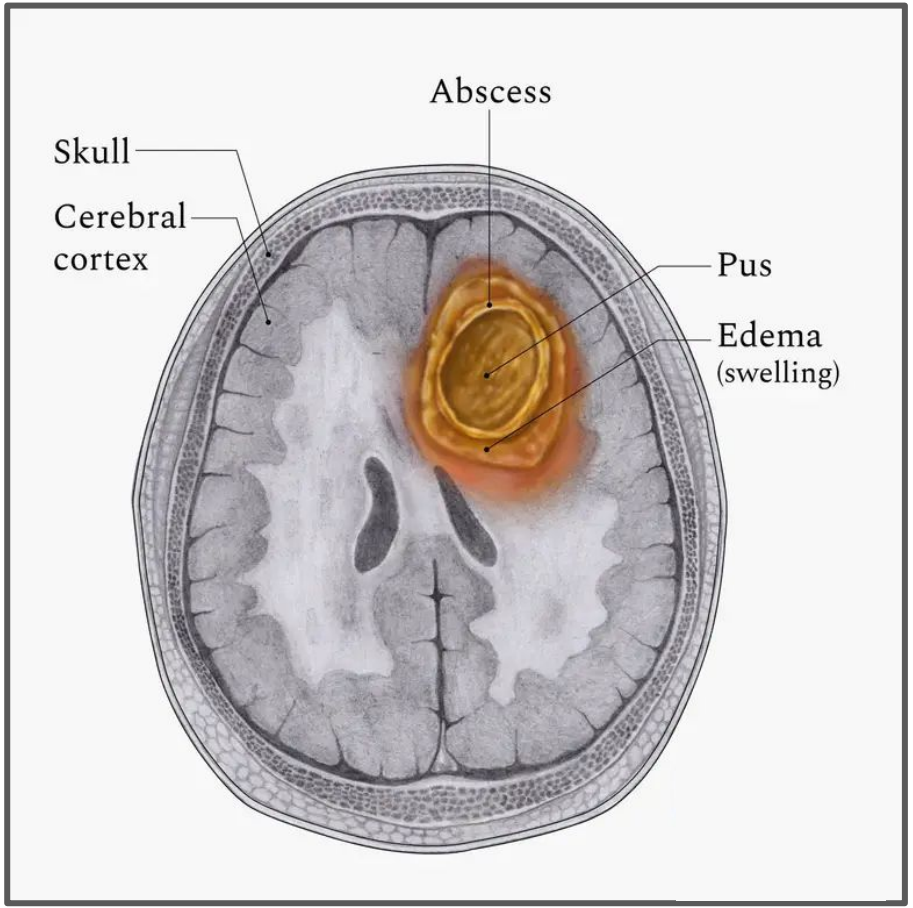
Listeria monocytogenes	Ampicillin or penicillin G(f)

f: Addition of an aminoglycoside(1st one week) should be considered.
Synergy and enhanced killing in vitro and in vivo(animal model).

Third-generation cephalosporins are inactive in meningitis caused by *L. monocytogenes*.

Hasbun R., Beek D. Acute meningitis. Mandell. 2020;1183-219

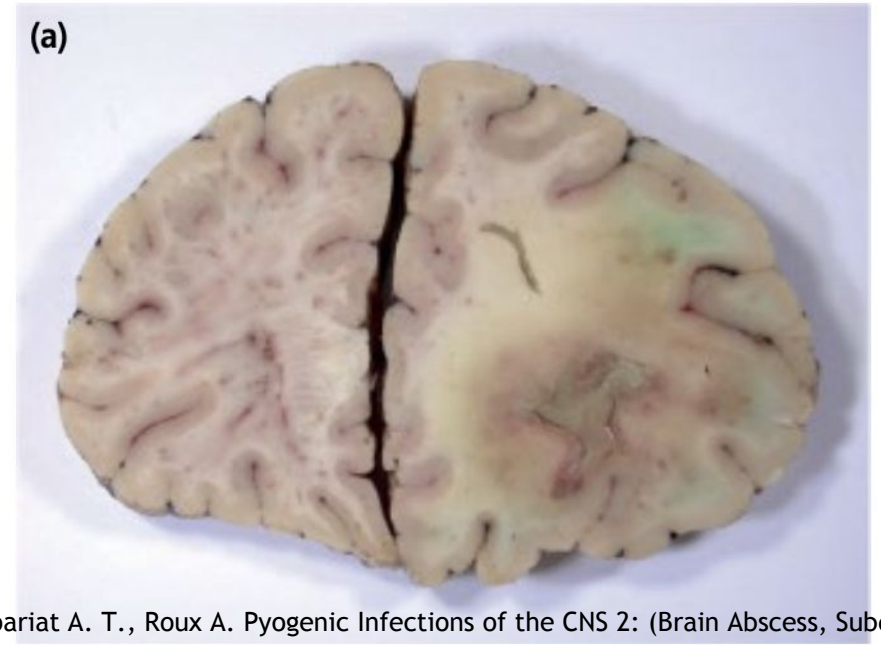
Brain abscess



Brain Abscess

Pyogenic

Pyogenic brain abscess : Gross pathology



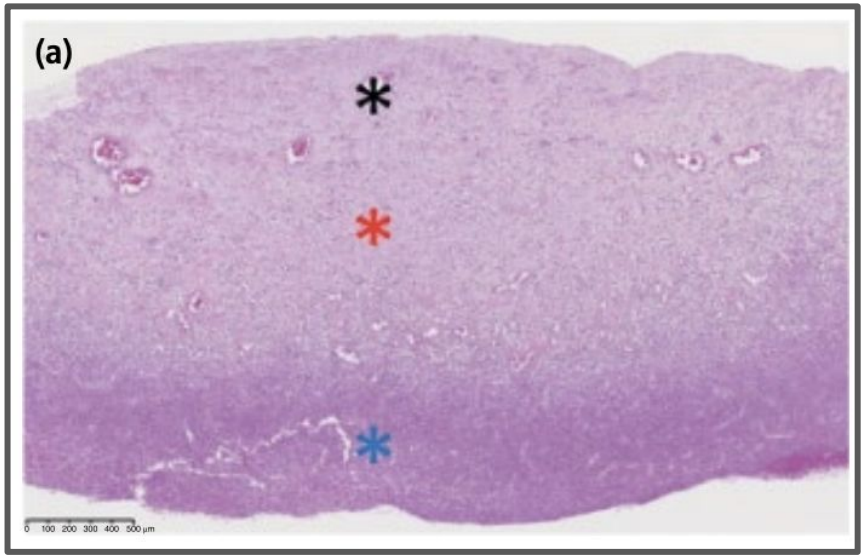
Focal necrotic lesion containing pus in its center in the white matter of the right frontal lobe, at the gray and white matter junction, surrounded by congestion.

Espariat A. T., Roux A. Pyogenic Infections of the CNS 2: (Brain Abscess, Subdural Abscess or Empyema, Epidural Abscess, Septic Embolism, and Suppurative Intracranial Phlebitis).Infections of the Central Nervous System: Pathology and Genetics. 2020; 309-18

Brain Abscess

Pyogenic

Pyogenic brain abscess : histopathology



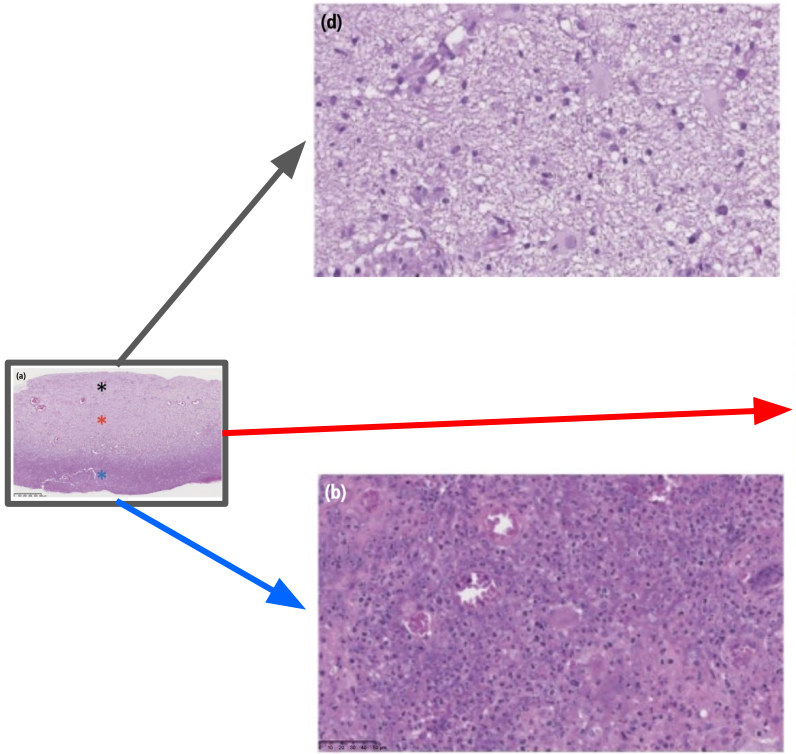
Low magnification showing different parts of the abscess:

(black asterisk)
An outer zone as the adjacent edematous brain parenchyma
(red asterisk)
The peripheral portion as granulation tissue the adjacent brain parenchyma
(blue asterisk)
the central portion as pus formation

Espariat A. T., Roux A. Pyogenic Infections of the CNS 2: (Brain Abscess, Subdural Abscess or Empyema, Epidural Abscess, Septic Embolism, and Suppurative Intracranial Phlebitis).Infections of the Central Nervous System: Pathology and Genetics. 2020; 309-18

Brain Abscess

Pyogenic



Outer zone of gliosis with reactive astrocytes and edema

Surrounding inflammatory granulation tissue with vascular and fibroblastic proliferation and chronic inflammatory cells

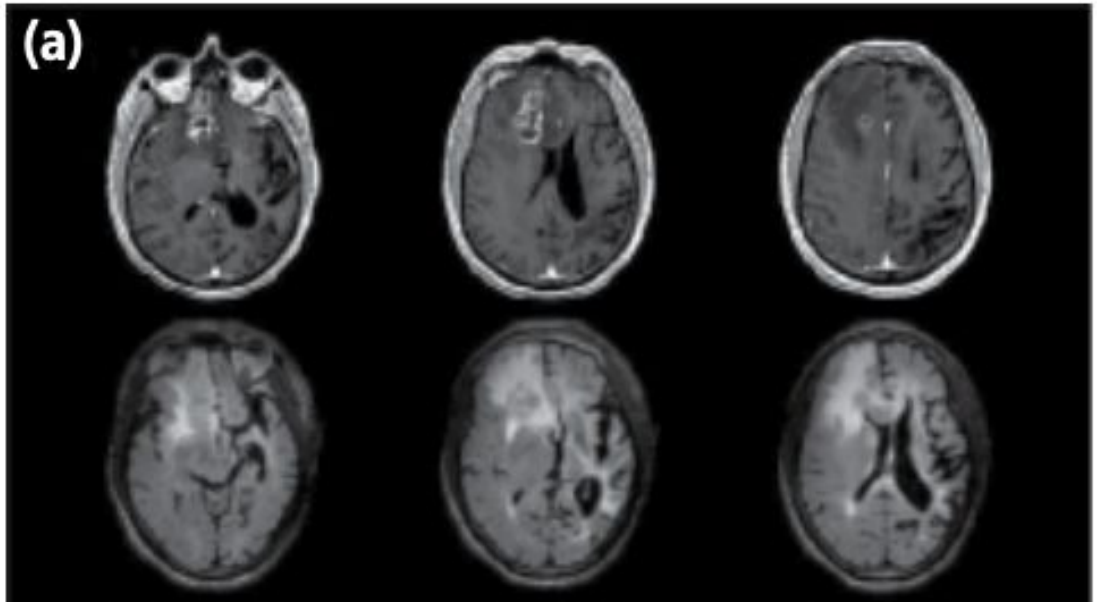
Central portion with numerous polymorphonuclear leukocytes

Espariat A. T., Roux A. Pyogenic Infections of the CNS 2: (Brain Abscess, Subdural Abscess or Empyema, Epidural Abscess, Septic Embolism, and Suppurative Intracranial Phlebitis).Infections of the Central Nervous System: Pathology and Genetics. 2020; 309-18

Brain Abscess

Pyogenic

Imaging

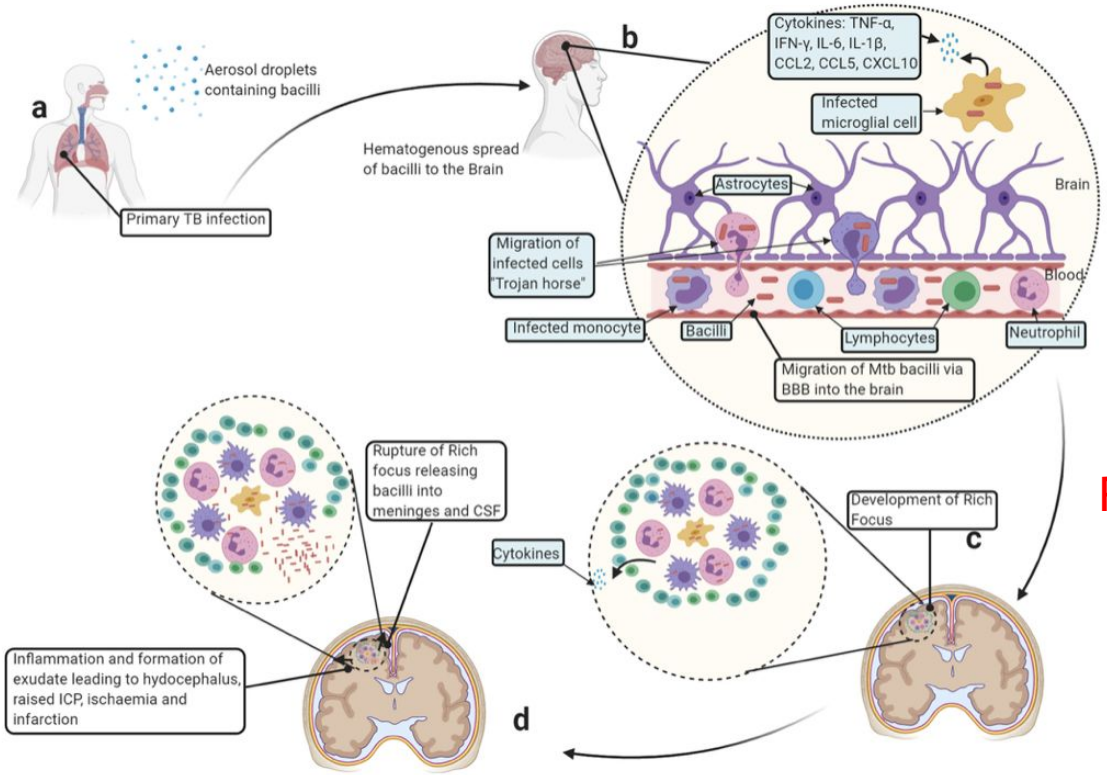


Brain MRI T1 with Gd demonstrated a right frontal enhancing mass with a central necrotic core and mass effect on the lateral ventricles. T2 FLAIR showed perilesional brain edema

Espariat A. T., Roux A. Pyogenic Infections of the CNS 2: (Brain Abscess, Subdural Abscess or Empyema, Epidural Abscess, Septic Embolism, and Suppurative Intracranial Phlebitis).Infections of the Central Nervous System: Pathology and Genetics. 2020; 309-18

Brain Abscess

Mycobacterium Tuberculosis



Pathogenesis

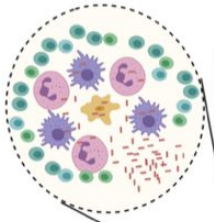
Rich Focus

Manyelo CM, Solomons RS, Walzl G, Chegou NN. Tuberculous Meningitis: Pathogenesis, Immune Responses, Diagnostic Challenges, and the Potential of Biomarker-Based Approaches. J Clin Microbiol. 2021;59(3).

Brain Abscess | Mycobacterium Tuberculosis

Pathogenesis

Rich Focus
(Subpial nodule)



Rupture → TB Meningitis

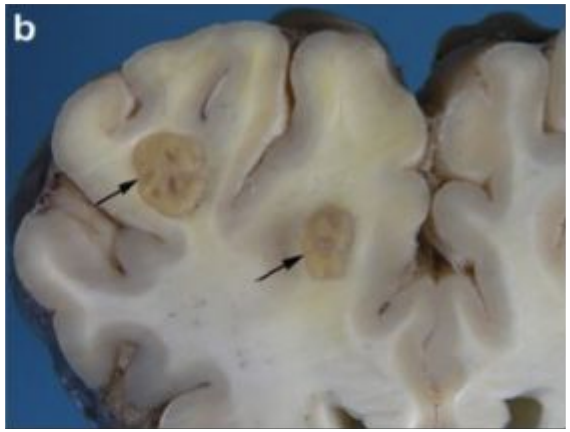
Enlarge → Tuberculoma

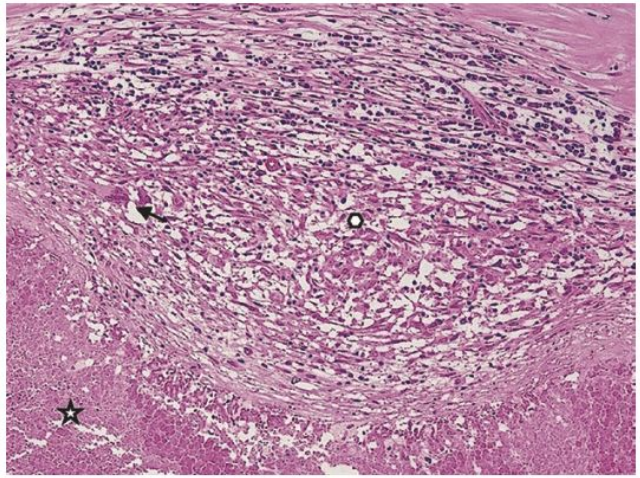
Enlarge → Tuberculous abscess

Malhotra K. P., Kulshreshtha D. Pathology of Tuberculosis of the Nervous System (Tuberculous Meningitis, Tuberculoma, Tuberculous Abscess). Tuberculosis of the Central Nervous System. 2017; 33-56

Brain Abscess | Mycobacterium Tuberculosis

Tuberculoma gross and histopathology



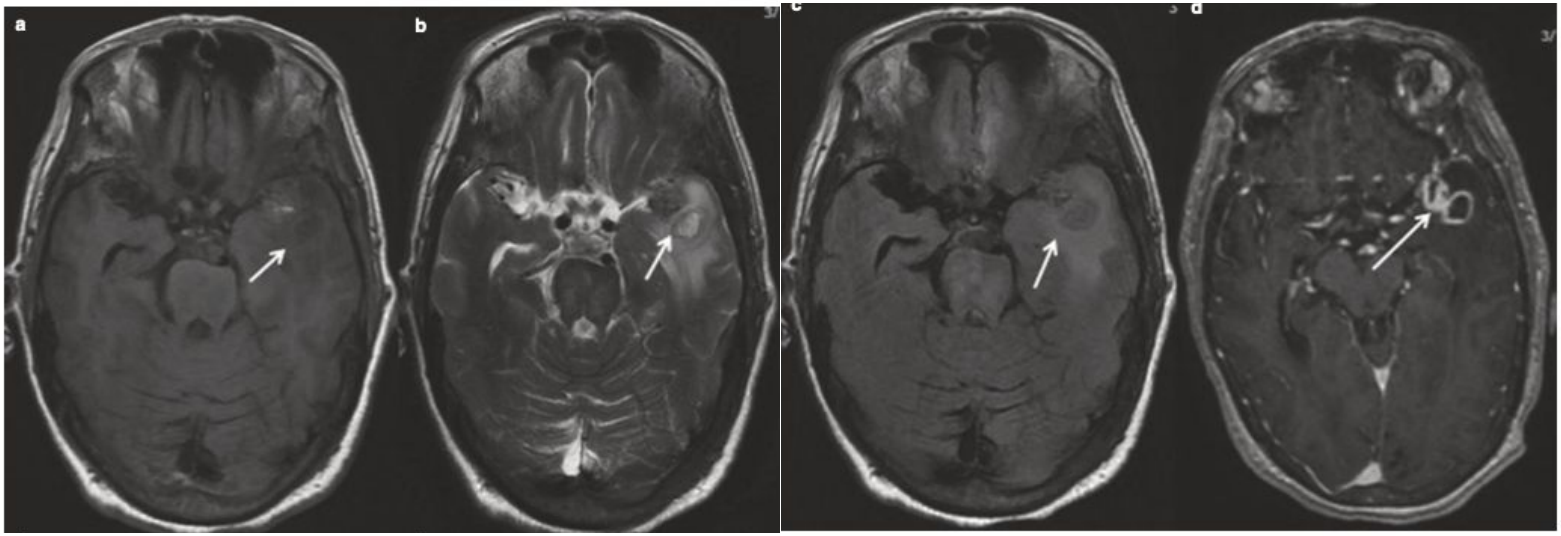


Caseous necrosis (*asterisk*) in the center of a granuloma (*circle*). Few multinucleated giant cells are noted (*arrow*)

Malhotra K. P., Kulshreshtha D. Pathology of Tuberculosis of the Nervous System (Tuberculous Meningitis, Tuberculoma, Tuberculous Abscess). Tuberculosis of the Central Nervous System. 2017; 33-56

Brain Abscess | Mycobacterium Tuberculosis

Tuberculoma imaging



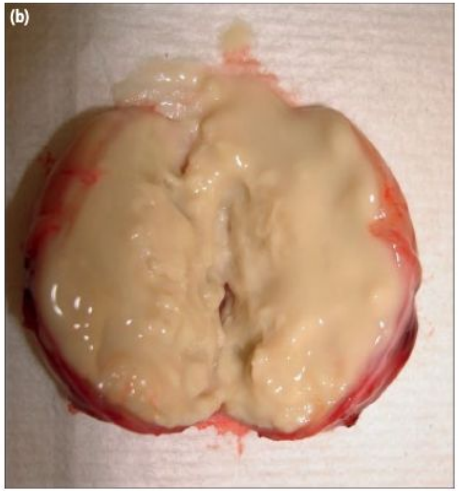
Axial T1 | Axial T2 | Axial T2 FLAIR | Axial T1 with Gd

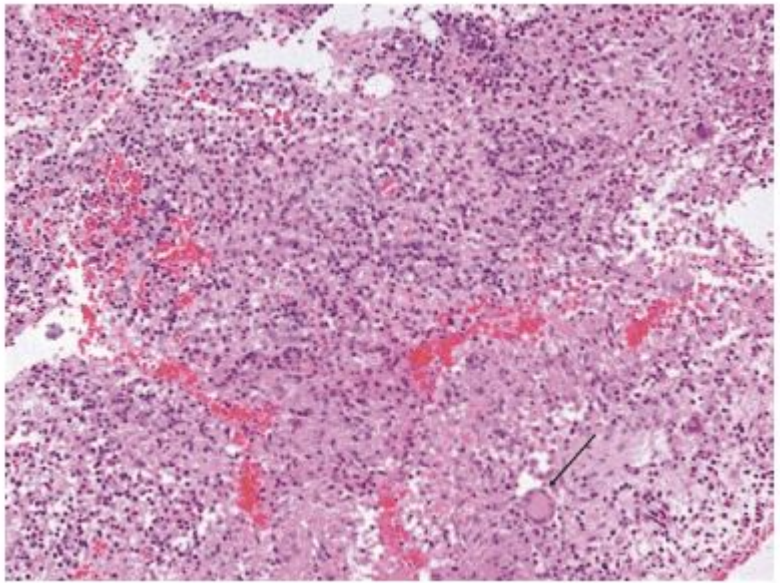
Malhotra K. P., Kulshreshtha D. Pathology of Tuberculosis of the Nervous System (Tuberculous Meningitis, Tuberculoma, Tuberculous Abscess). Tuberculosis of the Central Nervous System. 2017; 33-56

Brain Abscess

Mycobacterium Tuberculosis

Tuberculous abscess gross and histopathology



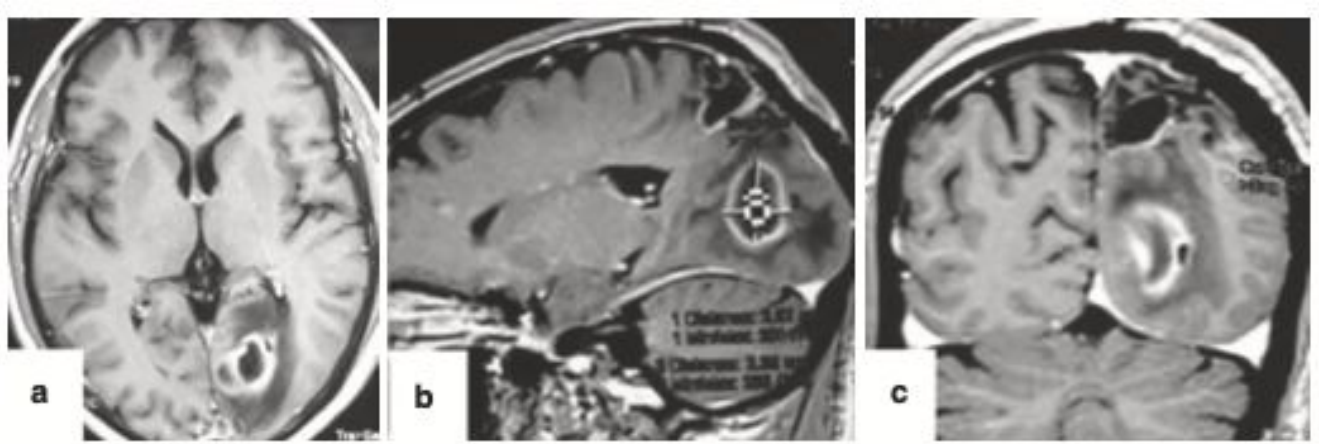


Intense mixed inflammation and occasional giant cells (*arrow*) in a section from tuberculous brain abscess

Malhotra K. P., Kulshreshtha D. Pathology of Tuberculosis of the Nervous System (Tuberculous Meningitis, Tuberculoma, Tuberculous Abscess). Tuberculosis of the Central Nervous System. 2017; 33-56

Brain Abscess | Mycobacterium Tuberculosis

Tuberculous abscess imaging



Contrast MRI of the brain; (a) axial images, (b) sagittal images, and (c) coronal images showing left parieto-occipital TBA

Malhotra K. P., Kulshreshtha D. Pathology of Tuberculosis of the Nervous System (Tuberculous Meningitis, Tuberculoma, Tuberculous Abscess). Tuberculosis of the Central Nervous System. 2017; 33-56

Brain Abscess

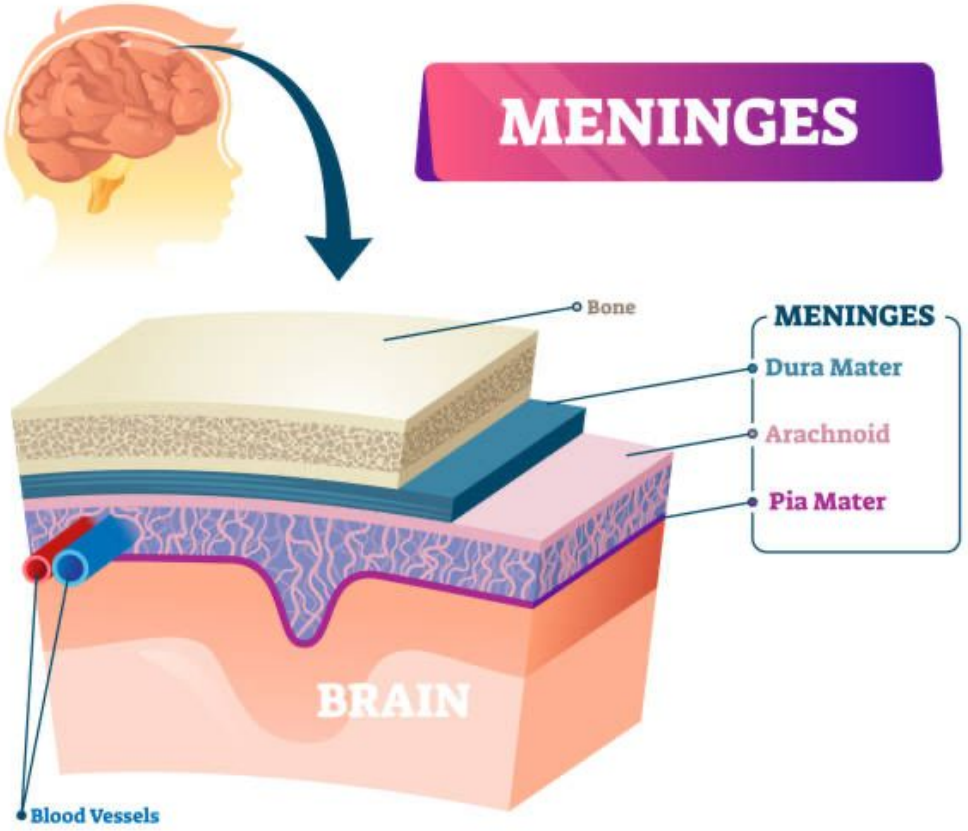
Mycobacterium Tuberculosis

Table 3: TBA versus tuberculoma

	TBA	Tuberculomas	
		Solid tuberculomas	Cystic tuberculomas
Clinical profile	Immunocompromised status	Immunocompetent patients. Past history of tuberculosis present	
Pathology[6,9]	Similar to PBA with the presence of polymorphonuclear leukocytic infiltrate in the wall. Absence of characteristic granulomatous reaction seen in TB	Typical granulomatous reaction, comprising of "epithelioid cells and giant cells" mixed with predominantly mononuclear cell infiltrate around a central area of necrosis	Characteristic granulomatous reaction at the periphery. Develop from liquefaction of caseous contents of a well-encapsulated tuberculoma, with a straw-colored fluid devoid of acute inflammatory component
MRI findings[10]	Circular or elliptical lesions, T1 hypo-intense, and T2 hyper-intense, with classical rim-enhancement on contrast administration	Conglomerate, solid, contrast-enhancing lesions with no central cystic area. Tuberculomas with caseation have T2 hypo-intense areas in the center (pathognomic)	Conglomerate, peripherally contrast-enhancing lesions with the central cystic area. However, walls are irregular and thick as compared to TBAs
Treatment[6]	Excision (if size >3 cm) or stereotactic aspiration followed by long duration (12-18 months) ATT (tailored to response)	Stereotactic biopsy and ATT for 12 months. Empirical ATT may be started based on clinical and radiological findings	

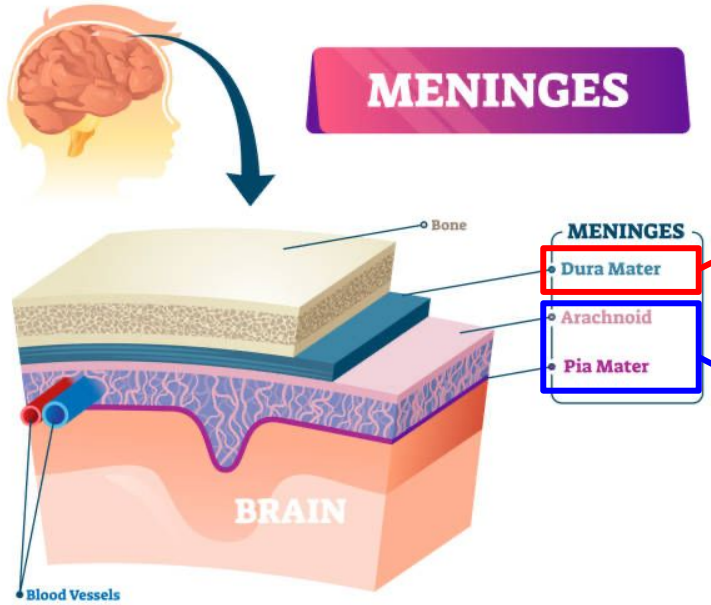
Mohindra S, Savardekar A, Gupta R, Tripathi M, Rane S. Tuberculous brain abscesses in immunocompetent patients: A decade long experience with nine patients. Neurol India. 2016;64(1):66-74.

Meningitis


MENINGES
Bone
MENINGES
Dura Mater
Arachnoid
Pia Mater
BRAIN
Blood Vessels

Meningitis

Definition : Meningitis, or inflammation of the meninges



Pachymeninges

Leptomeninges

Aksamit AJ, Jr., Berkowitz AL. Meningitis. Continuum (Minneap Minn). 2021;27(4):836-54.

Leptomeningitis

Pyogenic leptomeningitis

Pathogenesis and pathophysiology

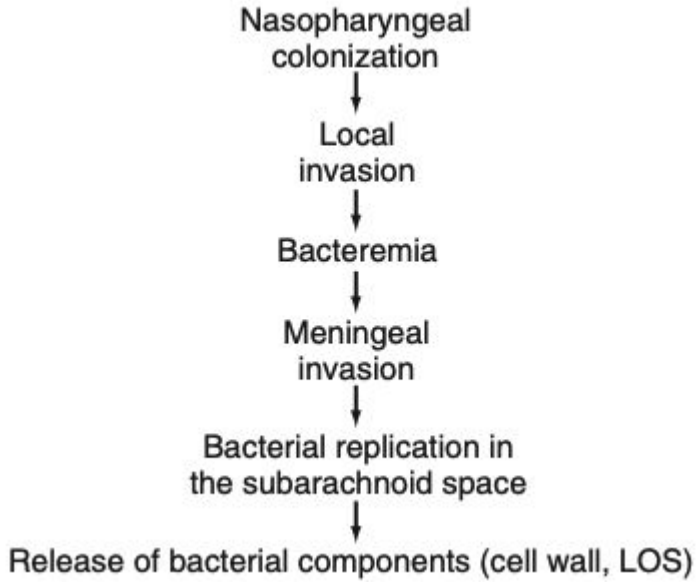


TABLE 87.6 Selected Factors Involved in the Pathogenesis of Bacterial Meningitis

PATHOGENIC EVENT	BACTERIAL FACTORS	HOST FACTORS
Mucosal colonization	Fimbriae, polysaccharide capsule, IgA protease production, bacteriocins	Mucosal epithelium, secretory IgA, ciliary activity, anticapsular antibodies, pilin phosphotransferase
Intravascular survival	Polysaccharide capsule	Complement activation, organism-specific antibodies, TLR-9 single nucleotide polymorphisms, migration inhibitory factor single nucleotide polymorphisms
Meningeal invasion	Fimbriae, association with monocytes, *ibe10*, OmpA, extracellular loops of OmpA, platelet-activating factor receptor, pneumococcal choline-binding protein A, lipoteichoic acid, listeriolysin O, choline-binding protein CbpA, RrgA	Blood-brain barrier, cytotoxic necrotizing factor-1, cysteinyl leukotrienes, biopterin, cytosolic phospholipase $A_2\alpha$, β_2-adrenoceptor
Survival in the subarachnoid space	Polysaccharide capsule	Poor opsonic activity

Hasbun R., Beek D. Acute meningitis. Mandell. 2020;1183-219

Leptomeningitis

Pyogenic leptomeningitis

Streptococcus pneumoniae
Neisseria meningitidis
Haemophilus influenzae

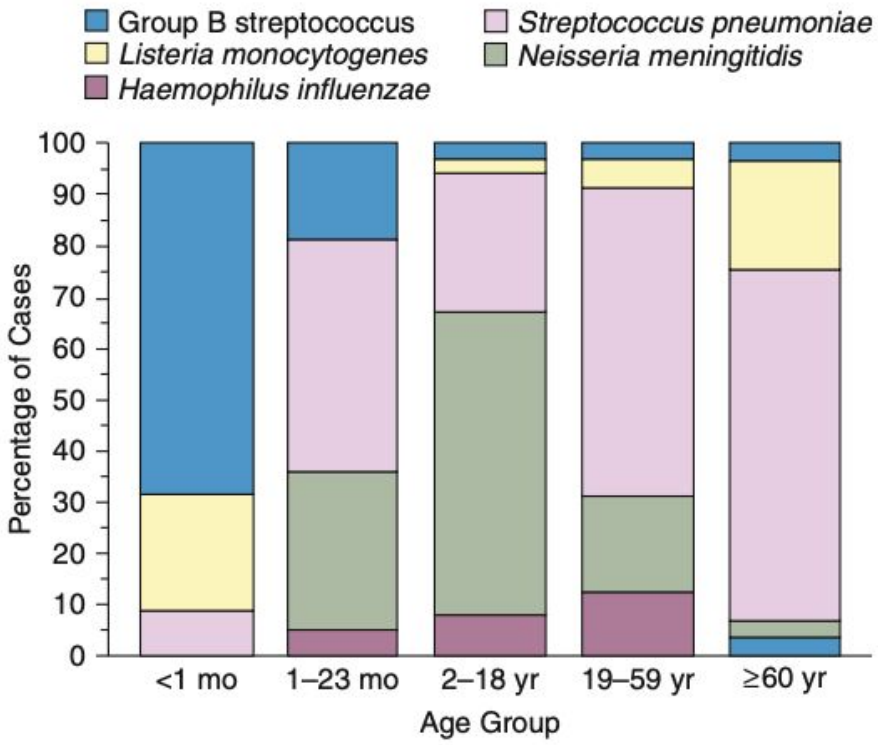
} Most common pathogen

Listeria monocytogenes
Gram negative bacilli(*Escherichia coli*, *Klebsiella* spp.)
Group B Streptococcus(*Streptococcus agalactiae*)
Staphylococcus aureus

Hasbun R., Beek D. Acute meningitis. Mandell. 2020;1183-219

Leptomeningitis

Pyogenic leptomeningitis

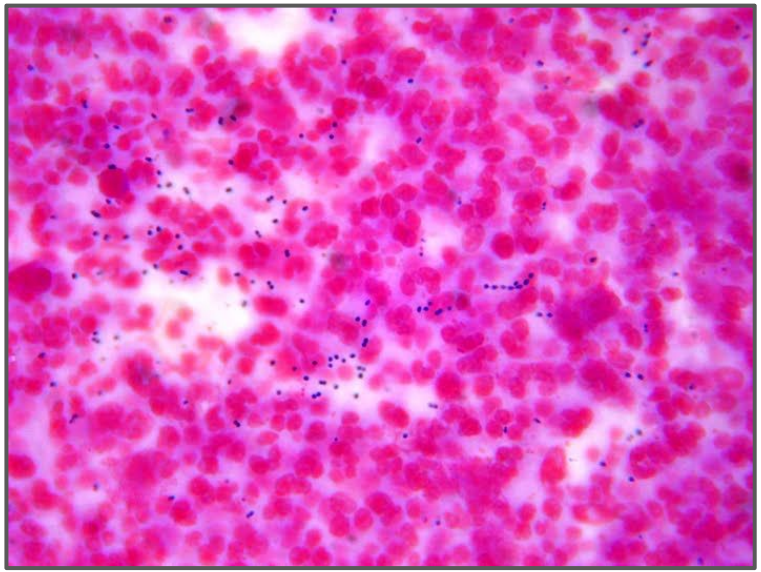


Archibald L., Quisling R. Acute Bacterial Meningitis. *Textbook of Neurointensive Care. 2013;430-47*

Leptomeningitis | Pyogenic | *S.pneumoniae*

***Streptococcus pneumoniae*(Most common pathogen)**

- Gram-positive, alpha-hemolytic, aerobic, encapsulated diplococci



Gram stain of CSF (X1000)

Gram positive cocci in pairs and short chains suggestive of *Streptococcus pneumoniae*

Archibald L., Quisling R. Acute Bacterial Meningitis.*Textbook of Neurointensive Care.*

Leptomeningitis | Pyogenic | *S.pneumoniae*

Treatment specific for *S.pneumoniae*

Streptococcus pneumoniae	
Penicillin MIC ≤0.06 µg/mL	Penicillin G or ampicillin
Penicillin MIC ≥0.12 µg/mL	
Ceftriaxone or cefotaxime MIC <1.0 µg/mL	Ceftriaxone or cefotaxime
Ceftriaxone or cefotaxime MIC ≥1.0 µg/mL	Vancomycin[c] plus ceftriaxone or cefotaxime

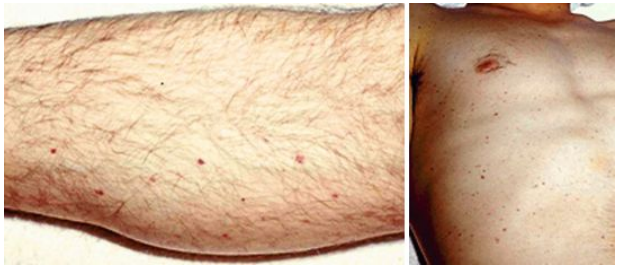
Duration : 10 - 14 days

Hasbun R., Beek D. Acute meningitis. Mandell. 2020;1183-219

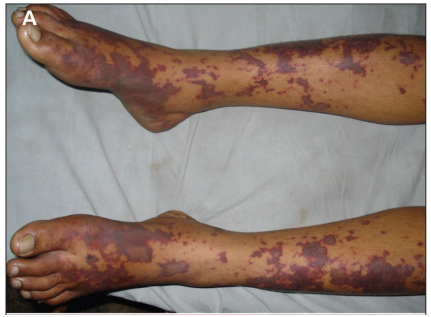
Leptomeningitis | Pyogenic | *N.meningitidis*

Neisseria meningitidis(meningococcal meningitis)

- Extracellular Gram-negative diplococci
- Systemic complications, such as septic shock, purpura fulminans, and DIC
- Droplet precaution



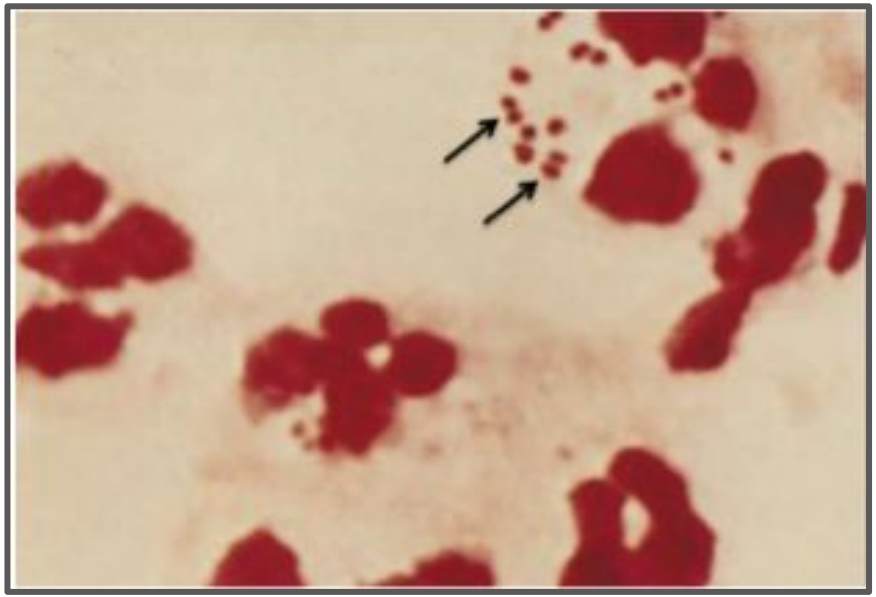
Petechial rash



Purpura fulminans
(Skin hemorrhagic necrosis)

Archibald L., Quisling R. Acute Bacterial Meningitis.*Textbook of Neurointensive Care.*

Leptomeningitis | Pyogenic | *N.meningitidis*



Gram stain of CSF
Gram Negative diplococci
suggest of *Neisseria meningitidis*

Archibald L., Quisling R. Acute Bacterial Meningitis.*Textbook of Neurointensive Care.*

Leptomeningitis | Pyogenic | *N.meningitidis*

Treatment specific for *N.meningitidis*

Duration : 7 days

Neisseria meningitidis	
Penicillin MIC <0.1 μg/mL	Penicillin G or ampicillin
Penicillin MIC 0.1–1.0 μg/mL	Ceftriaxone or cefotaxime

Hasbun R., Beek D. Acute meningitis. Mandell. 2020;1183-219

Chemoprophylaxis for Close contacts

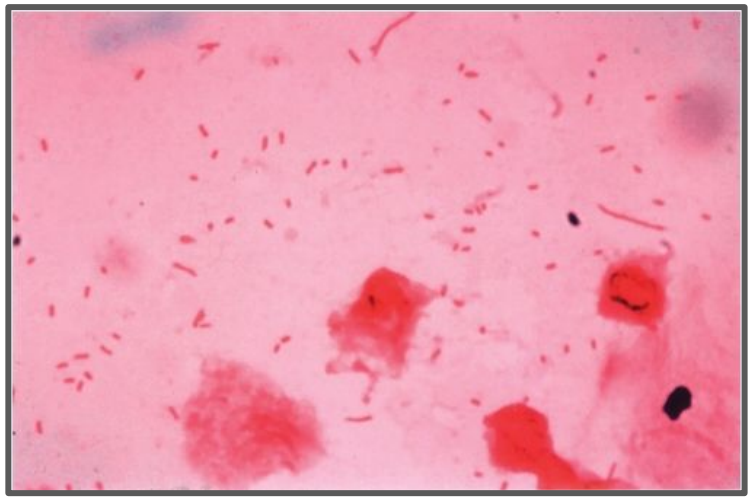
- Rifampicin 600 mg oral q 12 hr x 2 days
- Ceftriaxone 250 mg IM single dose
- Ciprofloxacin 500 mg oral single dose

MacNeil J, Patton M. Chapter 8: Meningococcal Disease. In: Roush S, Baldy L, eds. *Manual for the Surveillance of Vaccine-Preventable Diseases*. 5 ed. Atlanta, GA: Centers for Disease Control and Prevention; 2018.

Leptomeningitis | Pyogenic | *H.influenzae*

Haemophilus influenzae

- Encapsulated Gram-negative coccobacilli



Gram stain of CSF
Gram Negative coccobacilli, bacili
suggest of *Haemophilus influenzae*

Archibald L., Quisling R. Acute Bacterial Meningitis.*Textbook of Neurointensive Care.*

Leptomeningitis | Pyogenic | *H.influenzae*

Treatment specific for *H.influenzae*

Haemophilus influenzae	
β-Lactamase negative	Ampicillin
β-Lactamase positive	Ceftriaxone or cefotaxime

Duration : 7 - 10 days

Hasbun R., Beek D. Acute meningitis. Mandell. 2020;1183-219

Leptomeningitis | Pyogenic | *L.monocytogenes*

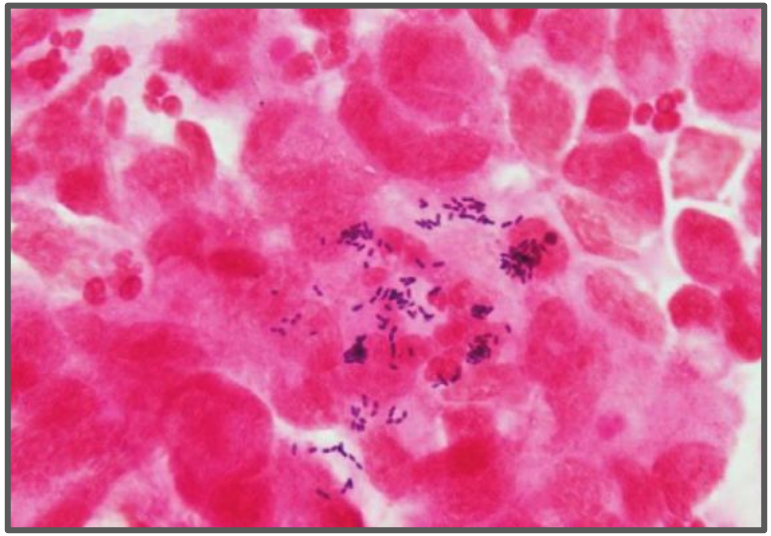
Listeria monocytogenes

- Gram positive bacilli(Intracellular/Extracellular)
- Risk factor : Neonate, Pregnant, Elderly(esp > 60 years old)
- Mortality rate of 15% to 29%
- Contaminate with raw vegetables, milk, cheese, and processed meats
- Pointing to the intestinal tract as the usual portal of entry.
- 30% Cause CSF Lymphocytic pleocytosis

Hasbun R., Beek D. Acute meningitis. Mandell. 2020;1183-219

Leptomeningitis | Pyogenic | *L.monocytogenes*

Gram stain of CSF : Gram Positive bacilli
suggest of *Listeria monocytogenes*



<u>Treatment specific for *L.monocytogenes*</u>

Ampicillin or penicillin G(f)
Duration : At least 21 days

f: Addition of an aminoglycoside(1st one week)
should be considered.
Synergy and enhanced killing in vitro and in vivo(animal model).

Third-generation cephalosporins are inactive in meningitis caused by *L. monocytogenes*.

Hasbun R., Beek D. Acute meningitis. Mandell. 2020;1183-219

Leptomeningitis | Pyogenic | *L.monocytogenes*

Duration : At least 21 days

Treatment specific for *L.monocytogenes*

Listeria monocytogenes	Ampicillin or penicillin G(f)

f: Addition of an aminoglycoside(1st one week) should be considered.
Synergy and enhanced killing in vitro and in vivo(animal model).

Third-generation cephalosporins are inactive in meningitis caused by *L. monocytogenes*.

Hasbun R., Beek D. Acute meningitis. Mandell. 2020;1183-219

Leptomeningitis | Pyogenic | *GNB*

Gram negative bacilli(*Escherichia coli*, *Klebsiella* spp.)

- Older adults, immunosuppressed patients, and patients with gram-negative septicemia
- Associated with disseminated strongyloidiasis in hyperinfection syndrome

Hasbun R., Beek D. Acute meningitis. Mandell. 2020;1183-219

Leptomeningitis	Pyogenic	GBS, S.aureus

Group B Streptococcus(*Streptococcus agalactiae*)

- Common in neonate and infant transmit during birth canal
- In adult, risk factor usually present

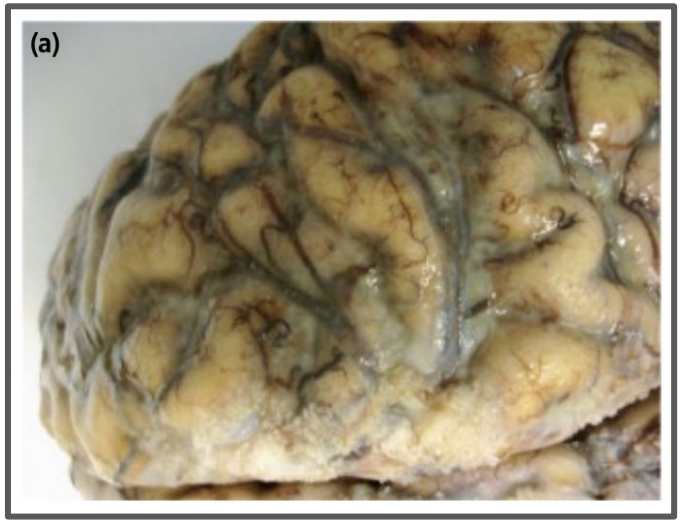
Staphylococcus aureus

- Associated with post-neurosurgical/post-trauma patients, CSF shunts and other underlying conditions include endocarditis, IVDU

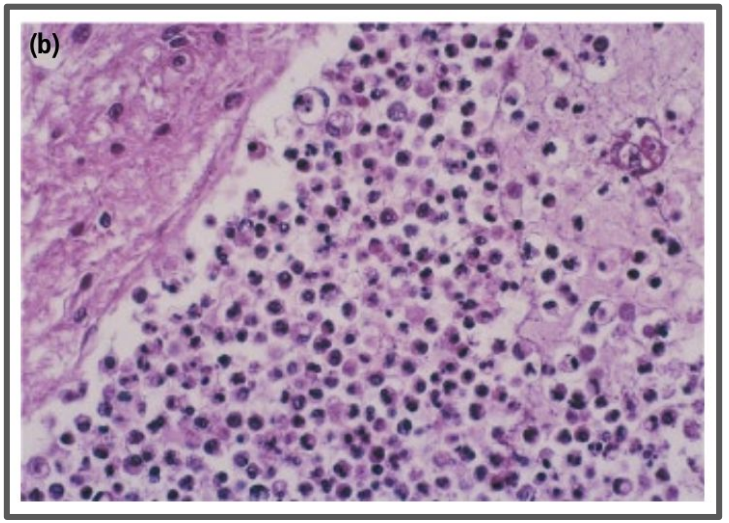
Hasbun R., Beek D. Acute meningitis. Mandell. 2020;1183-219

Leptomeningitis

Pyogenic leptomeningitis



Meningeal exudate in acute meningitis
Thin creamy lines of exudate alongside meningeal vessels

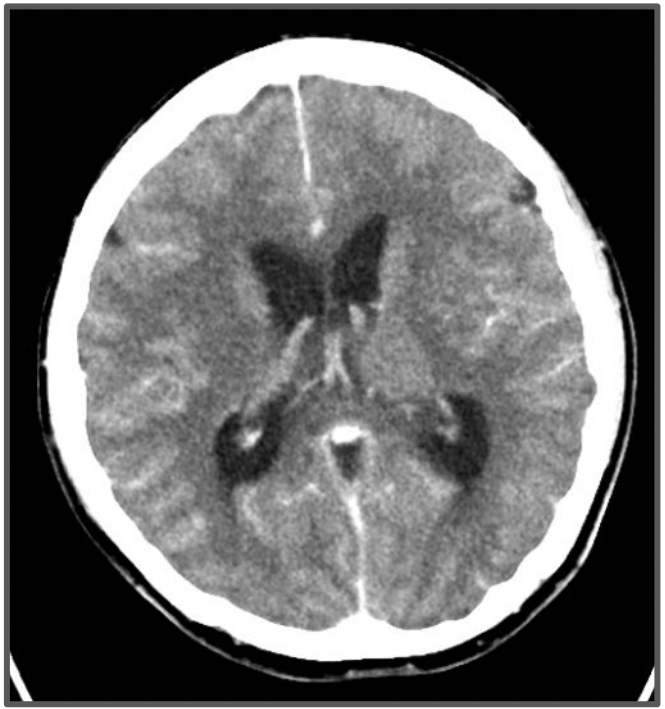


The meningeal cellular exudate is composed almost entirely of polymorphs and bacteria are both intracellular and extracellular.

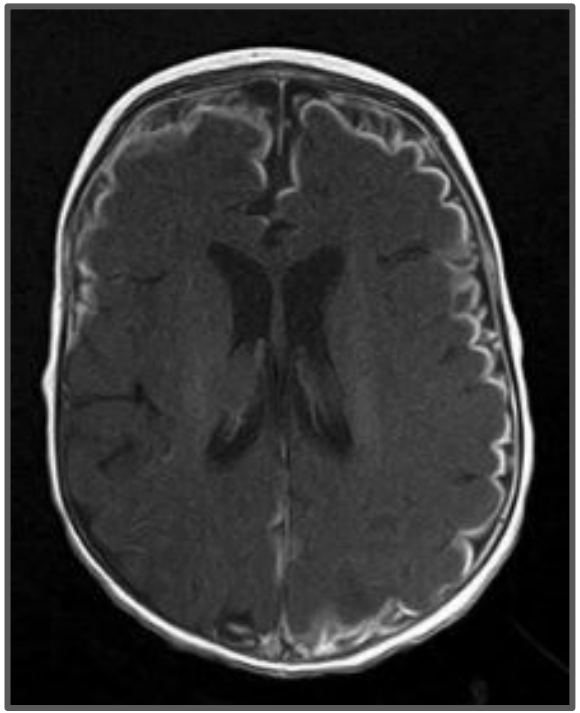
Guennec L. L., and Bourdoulous S. Pyogenic Infections of the CNS 1: Acute Bacterial Meningitis. Infections of the Central Nervous System: Pathology and Genetics. 2020; 295 – 308

Leptomeningitis

Pyogenic leptomeningitis



CT brain with contrast Axial view



MRI brain with Gd Axial view T1

Hasbun R., Beek D. Acute meningitis. Mandell. 2020;1183-219

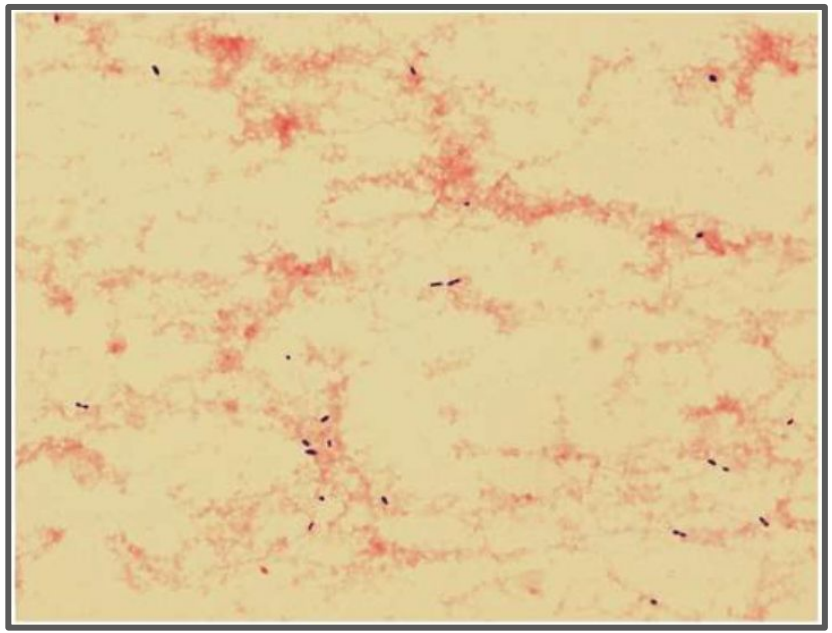
Leptomeningitis | Pyogenic | *S.suis*

Streptococcus suis

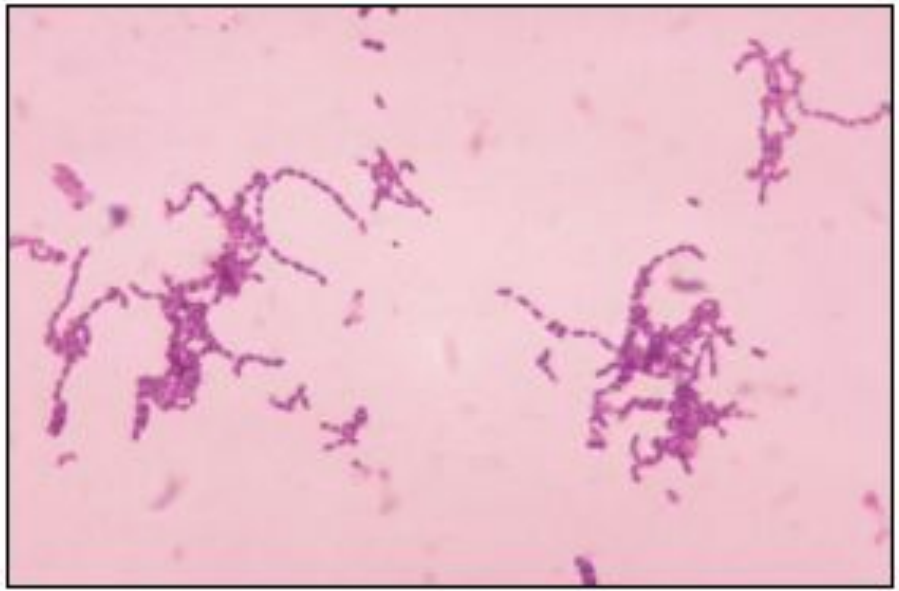
- Group D Streptococcus : Gram positive cocci in chain in serum
  : Gram positive diplococci in CSF
- Zoonotic Significant risk factor
  Exposure to pigs or pork (61%)
- The case fatality rate was 2.9%
- Acute to subacute symptom

Rayanakorn A, Goh BH, Lee LH, Khan TM, Saokaew S. Risk factors for Streptococcus suis infection: A systematic review and meta-analysis. Sci Rep.2018;8(1):13358.

Leptomeningitis Pyogenic *S.suis*



Gram positive diplococci in CSF



Gram positive cocci in chain in blood culture

Rayanakorn A, Goh BH, Lee LH, Khan TM, Saokaew S. Risk factors for Streptococcus suis infection: A systematic review and meta-analysis. Sci Rep.2018;8(1):13358.

Leptomeningitis | Pyogenic | *S.suis*

Clinical feature

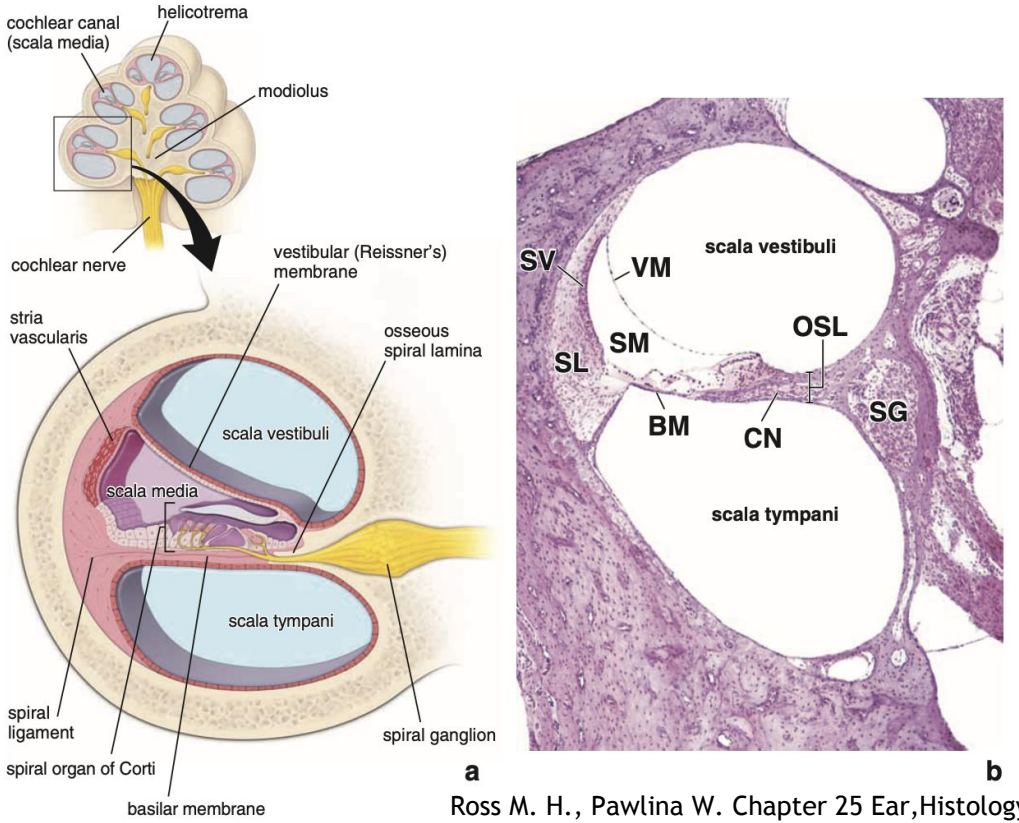
- Classical triad(Fever, stiff neck, Alteration of consciousness) : 9%
- Headache (95%)
- Fever (97%)
- Neck stiffness (93%)
- Altered consciousness (31%)
- Hearing loss (53%)[Sensorineural, Unilateral/Bilateral]

with or without vestibular dysfunction is thought to be attributed to direct infection of the cochlea. *S.suis* is believed to enter the perilymph via the cochlear aqueduct through the lytic action of exotoxins

Rayanakorn A, Goh BH, Lee LH, Khan TM, Saokaew S. Risk factors for Streptococcus suis infection: A systematic review and meta-analysis. Sci Rep.2018;8(1):13358.

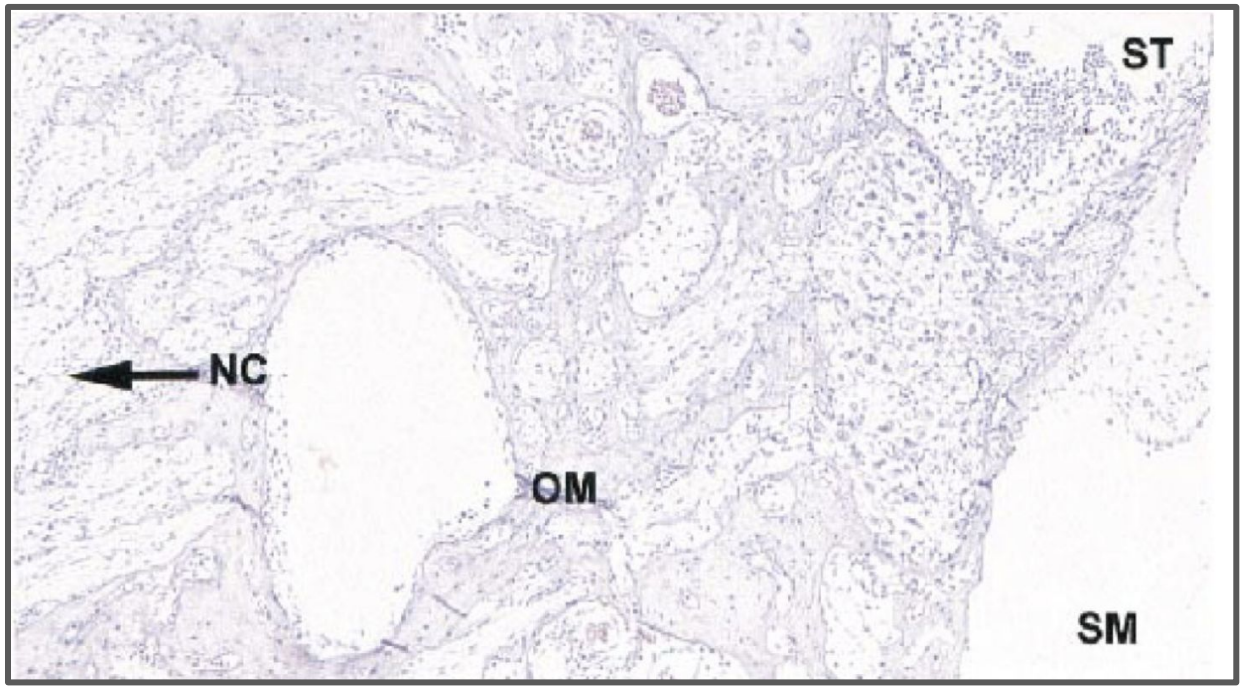
Leptomeningitis | Pyogenic | *S.suis*

Normal cochlear structure



Ross M. H., Pawlina W. Chapter 25 Ear,Histology a text and atlas 7th edition. 2016;936-61

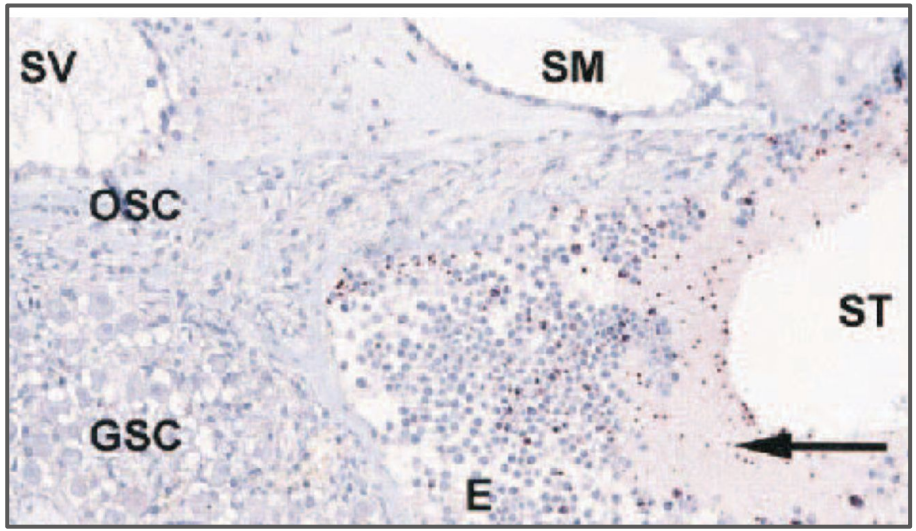
Leptomeningitis | Pyogenic | *S.suis*

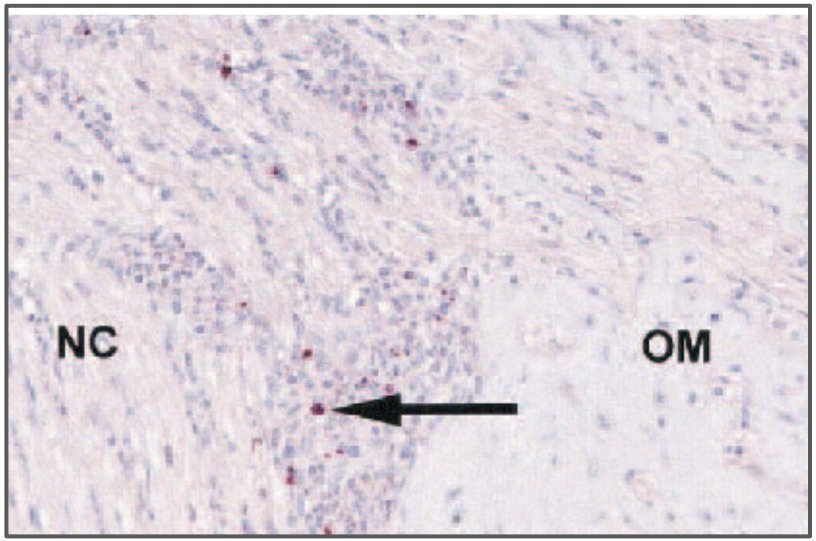


Exudate along the nervus cochlearis (←NC)
Exudate is evident in the scala tympani (ST) but not in the scala media (SM)

Madsen LW, Svensmark B, Elvestad K, Jensen HE. Otitis interna is a frequent sequela to Streptococcus suis meningitis in pigs. Vet Pathol. 2001;38(2):190-5.

Leptomeningitis | Pyogenic | *S.suis*

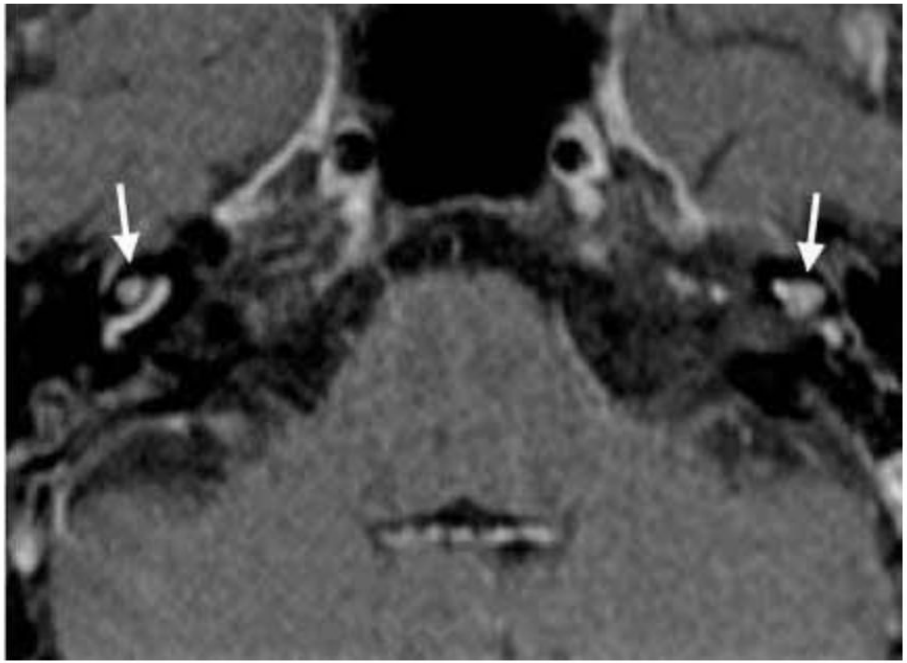




Labyrinthitis with mixed inflammatory cells and
Streptococcus suis serotype 2 antigen (arrow) in the exudate (E)

Madsen LW, Svensmark B, Elvestad K, Jensen HE. Otitis interna is a frequent sequela to Streptococcus suis meningitis in pigs. Vet Pathol. 2001;38(2):190-5.

Leptomeningitis | Pyogenic | *S.suis*



Enhanced TI -weighted MR image shows abnormal cochlear enhancement on both sides (arrows).

Tan JH, Yeh BI, Seet CS. Deafness due to haemorrhagic labyrinthitis and a review of relapses in Streptococcus suis meningitis. Singapore Med J. 2010;51(2):e30-3.

Leptomeningitis | Pyogenic | *S.suis*

Treatment

Streptococcus suis — Ceftriaxone or Penicillin G

Duration : (10 -) 14 days

Adjuvant Steroid**

- Dexamethasone 0.4 mg/kg twice a day x 4 days

Wertheim HF, Nghia HD, Taylor W, Schultsz C. Streptococcus suis: an emerging human pathogen. Clin Infect Dis. 2009;48(5):617-25.

Leptomeningitis

Pyogenic leptomeningitis

Diagnosis

Lumbar puncture

TABLE 87.10 Typical Cerebrospinal Fluid Findings in Patients With Bacterial Meningitis

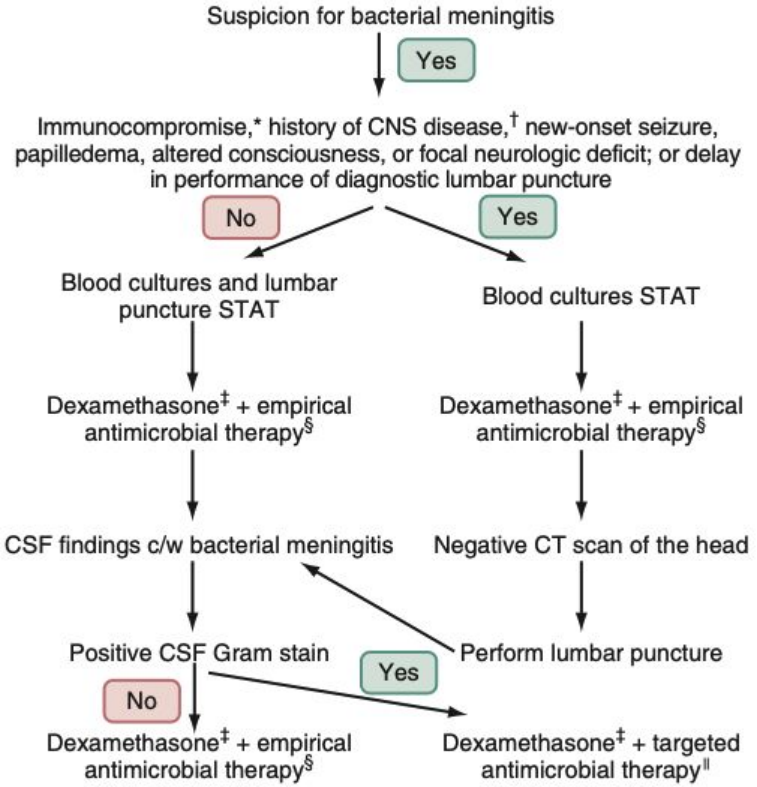
CSF PARAMETER	TYPICAL FINDING
Opening pressure	200–500 mm H_2O
White blood cell count	1000–5000/mm^3 (range, <100 to >10,000)
Percentage of neutrophils	≥80% (30% Lymphocyte predominated in L.monocytogenes)
Protein	100–500 mg/dL
Glucose	≤40 mg/dL
CSF-to-serum glucose ratio	≤0.4
Gram stain	Positive in 60%–90%
Culture	Positive in 70%–85%

CSF, Cerebrospinal fluid.

Hasbun R., Beek D. Acute meningitis. Mandell. 2020;1183-219

Leptomeningitis

Pyogenic leptomeningitis



Acute management

DON'T DELAY Antibiotic

Hasbun R., Beek D. Acute meningitis. Mandell. 2020;1183-219

Leptomeningitis

Pyogenic leptomeningitis

TABLE 2-2 **Empiric Antibiotic Therapy of Bacterial Meningitis**

Clinical context	Treatment
Adults	
Community acquired	Vancomycin 15-20 mg/kg IV every 8-12 hours (not to exceed 2 g per dose or a total daily dose of 60 mg/kg, adjust dose based on serum drug level to target trough) until sensitivities of organism are known AND Ceftriaxone 2 g IV every 12 hours or cefotaxime 2 g IV every 4-6 hours AND Dexamethasone 10 mg IV every 6 hours for 4 days
Alcohol use disorder or advanced age (>65 years old) or immunosuppression	Above treatment plus ampicillin 2 g IV every 4 hours (for *Listeria*) or, for patients who are allergic to penicillin, trimethoprim-sulfamethoxazole 10-20 mg/kg/d (trimethoprim component) IV divided every 6-12 hours
Neurosurgical procedure, shunt infection, or head trauma	Vancomycin (above doses) plus an antipseudomonal beta-lactam (such as cefepime 2 g IV every 8 hours, ceftazidime 2 g IV every 8 hours, or meropenem 2 g IV every 8 hours

Aksamit AJ, Jr., Berkowitz AL. Meningitis. Continuum (Minneap Minn). 2021;27(4):836-54.

Leptomeningitis

Pyogenic leptomeningitis

TABLE 87.13 Specific Antimicrobial Therapy for Acute Meningitis

MICROORGANISM	STANDARD THERAPY	ALTERNATIVE THERAPIES[a]
Bacteria		
Haemophilus influenzae		
β-Lactamase negative	Ampicillin	Ceftriaxone or cefotaxime or cefepime or chloramphenicol or aztreonam or a fluoroquinolone[b]
β-Lactamase positive	Ceftriaxone or cefotaxime	Cefepime or chloramphenicol or aztreonam or a fluoroquinolone[b]
Neisseria meningitidis		
Penicillin MIC <0.1 μg/mL	Penicillin G or ampicillin	Ceftriaxone or cefotaxime or chloramphenicol
Penicillin MIC 0.1–1.0 μg/mL	Ceftriaxone or cefotaxime	Chloramphenicol or a fluoroquinolone[b] or meropenem
Streptococcus pneumoniae		
Penicillin MIC ≤0.06 μg/mL	Penicillin G or ampicillin	Ceftriaxone or cefotaxime or chloramphenicol
Penicillin MIC ≥0.12 μg/mL		
Ceftriaxone or cefotaxime MIC <1.0 μg/mL	Ceftriaxone or cefotaxime	Meropenem or cefepime
Ceftriaxone or cefotaxime MIC ≥1.0 μg/mL	Vancomycin[c] plus ceftriaxone or cefotaxime	Vancomycin plus moxifloxacin[d]
Enterobacteriaceae[e]	Ceftriaxone or cefotaxime	Aztreonam or a fluoroquinolone[b] or trimethoprim-sulfamethoxazole or meropenem or ampicillin
Pseudomonas aeruginosa	Ceftazidime or cefepime	Aztreonam or a fluoroquinolone[b] or meropenem
Acinetobacter baumannii[e]	Meropenem	Colistin (usually formulated as colistimethate sodium)[g] or polymyxin B[g]
Listeria monocytogenes	Ampicillin or penicillin G[f]	Trimethoprim-sulfamethoxazole
Streptococcus agalactiae	Ampicillin or penicillin G[f]	Ceftriaxone or cefotaxime or vancomycin
Staphylococcus aureus		
Methicillin-sensitive	Nafcillin or oxacillin	Vancomycin or linezolid or daptomycin
Methicillin-resistant	Vancomycin[c]	Trimethoprim-sulfamethoxazole or linezolid or daptomycin or ceftaroline
Staphylococcus epidermidis	Vancomycin[c]	Linezolid

Hasbun R., Beek D. Acute meningitis. Mandell. 2020;1183-219

Leptomeningitis

Pyogenic leptomeningitis

TABLE 87.14 Recommended Dosages of Antimicrobial Agents for Bacterial Meningitis in Adults With Normal Renal and Hepatic Function

ANTIMICROBIAL AGENT	TOTAL DAILY DOSE	DOSING INTERVAL (h)
Amikacin[a]	15 mg/kg	8
Ampicillin	12 g	4
Aztreonam	6–8 g	6–8
Cefepime	6 g	8
Cefotaxime	8–12 g	4–6
Ceftaroline	1800 mg	8
Ceftazidime	6 g	8
Ceftriaxone	4 g	12–24
Chloramphenicol[b]	4–6 g	6
Ciprofloxacin	800–1200 mg	8–12
Daptomycin	6–10 mg/kg	24
Gentamicin[a]	5 mg/kg	8
Linezolid	1200 mg	12
Meropenem	6 g	8
Moxifloxacin[c]	400 mg	24
Nafcillin	12 g	4
Oxacillin	12 g	4
Penicillin G	24 million units	4
Rifampin	600 mg	12–24
Tobramycin[a]	5 mg/kg	8
Trimethoprim-sulfamethoxazole[d]	10–20 mg/kg	6–12
Vancomycin[e]	30–45 mg/kg	8–12

[a]Need to monitor peak and trough serum concentrations.
[b]Higher dose recommended for pneumococcal meningitis.
[c]No data on optimal dosage for patients with bacterial meningitis.
[d]Dosage based on trimethoprim component; many experts would use a dose of 5 mg/kg every 8 hours.
[e]Maintain serum trough concentrations of 15–20 µg/mL; one study recommended continuous infusion of 60 mg/kg/day (see text for details).
Modified from Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis. *2004;39:1267–1284.*

Hasbun R., Beek D. Acute meningitis. Mandell. 2020;1183-219

Leptomeningitis

Pyogenic leptomeningitis

TABLE 2-3 **Duration of Antibiotic Therapy for Meningitis Caused by Bacterial Organisms**[a]

Organism	Duration of therapy (days)
Streptococcus pneumoniae	10-14
Listeria monocytogenes	21
Neisseria meningitidis	7
Staphylococcus	Variable
Gram-negative bacilli	21
Group B *Streptococcus*	14-21
Haemophilus influenzae	7-10

[a] Data from Wilson JW, Oxford University Press.[20]

Aksamit AJ, Jr., Berkowitz AL. Meningitis. Continuum (Minneap Minn). 2021;27(4):836-54.

Leptomeningitis Viral

Pathogenesis and pathophysiology

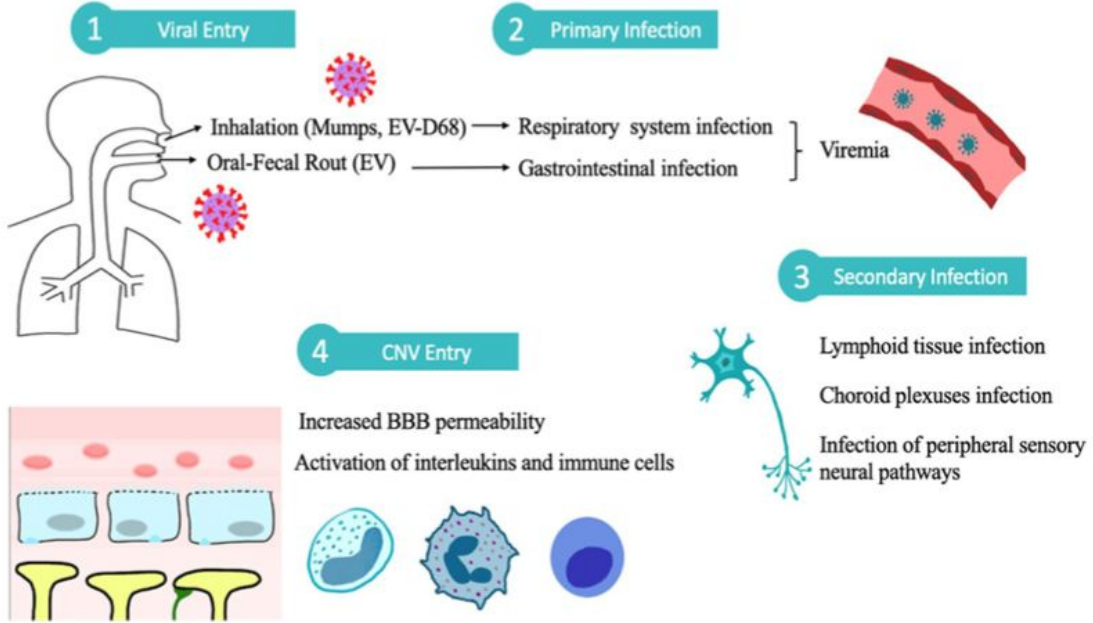


Fig. 1 Schematic presentation of the general features of viral meningitis pathogenesis

Kohil A, Jemmieh S, Smatti MK, Yassine HM. Viral meningitis: an overview. Arch Virol. 2021;166(2):335-45.

Leptomeningitis Viral

Pathogen

- Non-polio enteroviruses : enterovirus, echovirus, and coxsackievirus
- Herpes simplex virus
- Varicella-zoster virus
- Arboviruses
- Mumps virus
- Lymphocytic choriomeningitis virus
- Human immunodeficiency virus
- Severe acute respiratory syndrome coronavirus 2(SAR-COV2)
- Adenovirus

Hasbun R., Beek D. Acute meningitis. Mandell. 2020;1183-219

Leptomeningitis | Viral | Enteroviruses,HSV

Non-polio enteroviruses

- Enterovirus, Echovirus, and Coxsackievirus

- seasonal peak in the late summer months. Many serotypes of enterovirus

Herpes simplex virus

- HSV-2 more commonly causes meningitis(HSV-1 more commonly causes encephalitis)

- Recurrent meningitis secondary to HSV-2 can occur (Mollaret meningitis).

Hasbun R., Beek D. Acute meningitis. Mandell. 2020;1183-219

Leptomeningitis | Viral | VZV, HIV

Varicella-zoster virus(VZV)

- VZV can emerge from latency in the dorsal root ganglia and cause shingles (painful dermatomal vesicular rash) or meningitis

- Zoster meningitis can occur with or without concurrent rash.

Human immunodeficiency virus(HIV)

- most commonly at or around the time of seroconversion

- Serum HIV antibody testing may be negative, requiring viral load for confirmation.

Hasbun R., Beek D. Acute meningitis. Mandell. 2020;1183-219

Leptomeningitis Viral

Investigation

CSF profile

Organism	Protein, mg/dL	Glucose	White blood cells/mm^3	Cell type predominance
Viral meningitis	<120	>40% serum[a]	10-500	Lymphocytes

[a] Decreased CSF glucose may be seen in some viral infections causing meningitis.

HSV-2,HSV-1

Some evidence of no CSF pleocytosis

Aksamit AJ, Jr., Berkowitz AL. Meningitis. Continuum (Minneap Minn). 2021;27(4):836-54.

Leptomeningitis Viral

Investigation

CSF profile

Some Common Causes of Viral Meningitis TABLE 2-4

Viruses best diagnosed by polymerase chain reaction (PCR) in spinal fluid

- Herpes simplex type 2
- Enteroviruses including echoviruses, coxsackieviruses, and polioviruses
- Human parechovirus
- Varicella-zoster virus (VZV)[a]
- Cytomegalovirus
- Lymphocytic choriomeningitis virus (with accompanying IgM in the serum)

Viruses best diagnosed by serology in spinal fluid

- West Nile virus (IgM)
- La Crosse encephalitis virus (IgM)
- Mumps virus (IgM)

IgM = immunoglobulin M.
[a] For VZV vasculitis and myelitis, VZV IgG may be more sensitive than PCR.

Aksamit AJ, Jr., Berkowitz AL. Meningitis. Continuum (Minneap Minn). 2021;27(4):836-54.

Leptomeningitis Viral

Treatment

- HSV and VZV meningitis are generally treated with

  Acyclovir 10 - 15 mg/kg IV q 8 hrs In

  then switch to oral valacyclovir (1 gm oral bid) or famciclovir

  Total length of treatment is generally 10 to 14 days.

  Immunocompetent, the benefit is not clearly established.

  A 14-day course of IV therapy is recommended for meningitis in patients who are immunocompromised.

- Other pathogen : Self limited

Aksamit AJ, Jr., Berkowitz AL. Meningitis. Continuum (Minneap Minn). 2021;27(4):836-54.

Leptomeningitis Viral

Treatment

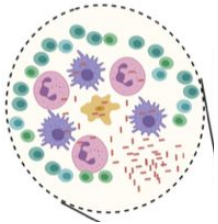
- Adjunctive therapy
  - >> Intravenous immunoglobulin(IVIG)
    - >> No establish benefit and result are varies
    - >> Consider in Immunoglobulin defect/dysfunction/disease
  - >> Steroid : no role in viral “Meningitis”

Hasbun R., Beek D. Acute meningitis. Mandell. 2020;1183-219

Leptomeningitis Mycobacterium Tuberculosis

Pathogenesis

Rich Focus
(Subpial nodule)



Rupture → TB Meningitis

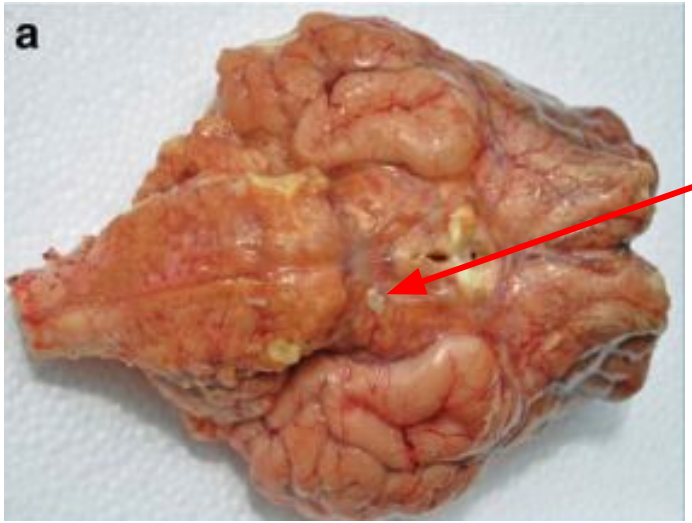
Enlarge → Tuberculoma

Enlarge → Tuberculous abscess

Malhotra K. P., Kulshreshtha D. Pathology of Tuberculosis of the Nervous System (Tuberculous Meningitis, Tuberculoma, Tuberculous Abscess). Tuberculosis of the Central Nervous System. 2017; 33-56

Leptomeningitis Mycobacterium Tuberculosis

Gross pathology

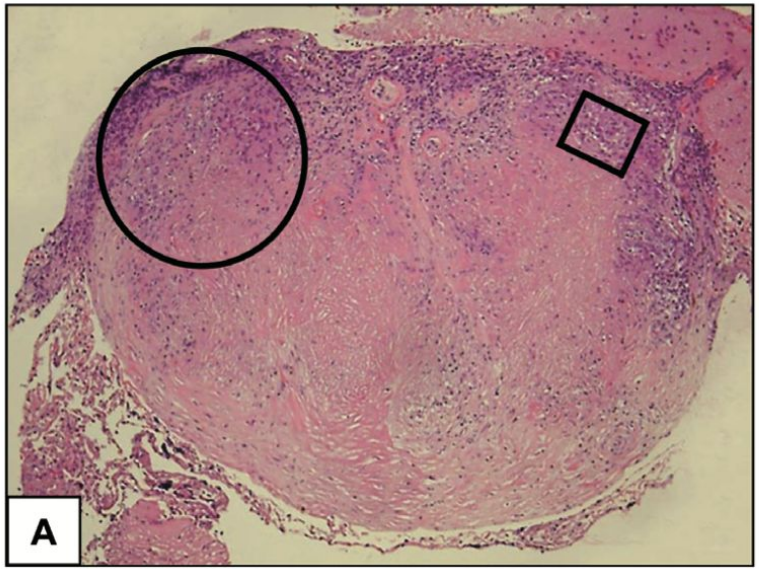


Leptomeninges of the basilar brain were severely thickened with a nodular and yellowish aspect.

Konradt G, Bassuino DM, Bianchi MV, Bandinelli MB, Driemeier D, Pavarini SP. Neurotuberculosis in cattle in southern Brazil. Trop Anim Health Prod. 2016;48(5):1089-94.

Leptomeningitis Mycobacterium Tuberculosis

Histopathology



(A)Nodular lesions showing caseous granulomas and advanced fibrosis.

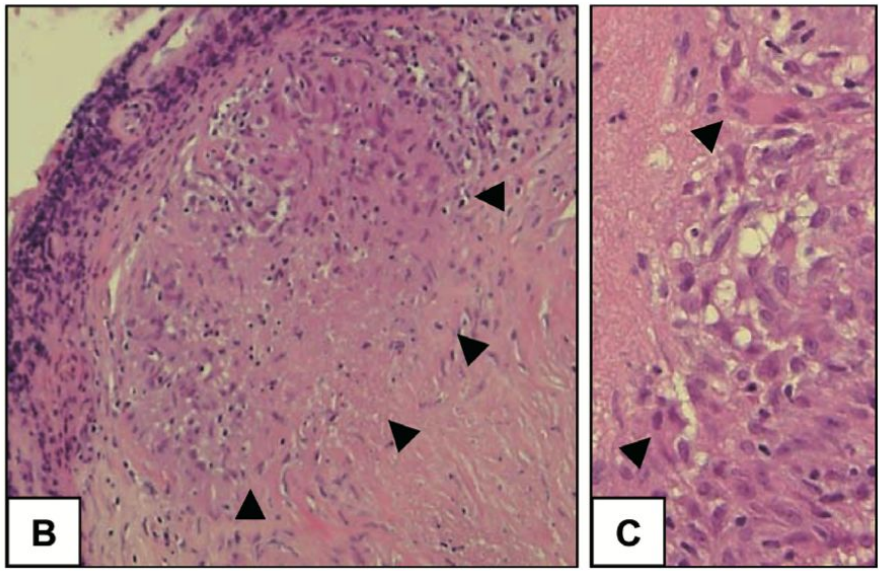
Tojo K, Yazaki M, Machida K, Sano K, Yoshida K, Ikeda S. Biopsy-proven tuberculous meningitis mimicking CNS sarcoidosis. Intern Med. 2007;46(24):2001-5.

Leptomeningitis Mycobacterium Tuberculosis

Histopathology

(B) Showing a caseous granuloma surrounded by many spindle-type epithelioid cells and lymphocytes.

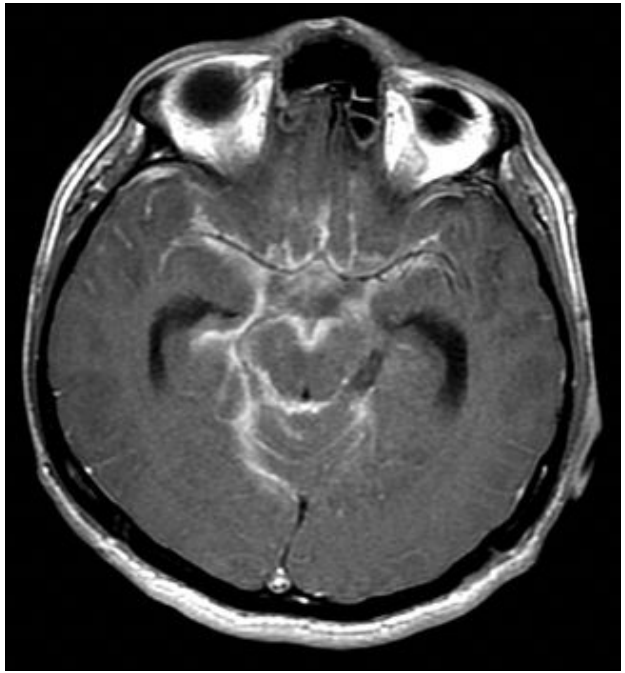
(C) Many spindle-type epithelioid cells,lymphocytes and some Langhans type multinucleated giant cells



Tojo K, Yazaki M, Machida K, Sano K, Yoshida K, Ikeda S. Biopsy-proven tuberculous meningitis mimicking CNS sarcoidosis. Intern Med. 2007;46(24):2001-5.

Leptomeningitis Mycobacterium Tuberculosis

Imaing



MRI T1 Post contrast show basal arachnoiditis in TB meningitis

Tojo K, Yazaki M, Machida K, Sano K, Yoshida K, Ikeda S. Biopsy-proven tuberculous meningitis mimicking CNS sarcoidosis. Intern Med. 2007;46(24):2001-5.

Take home message

- Route of CNS invasion and cellular tropism
  are the basis of pathogenesis

- Gross and histopathology
  lead to understand a radiological and clinical manifestation

Thank you