

Initial Approach to Meningoencephalitis



선우준상

순천향대 서울병원 신경과

Introduction

❖ Meningoencephalitis

❖ Infection

- Acute bacterial meningitis
- Viral meningitis, encephalitis
- Brain abscess, Subdural empyema
- Infectious thrombophlebitis.

❖ Inflammation

- Autoimmune encephalitis (NMDA, VGKC)
- Paraneoplastic limbic encephalitis
- Demyelinating diseases (ADEM)
- CNS vasculitides

❖ Other conditions mimicking meningoencephalitis

- Encephalopathy
- Leptomeningeal carcinomatosis, lymphomatosis
- Non-convulsive status epilepticus

Introduction

- ❖ Early recognition, efficient decision making, and rapid institution of therapy → **Lifesaving!**
 - Prodrome: fever and headache
 - Presentation: altered consciousness, focal neurologic deficits, or newly-onset seizures
 - Non-specific findings
- ✓ **Initial differential diagnosis**
- ✓ **Laboratory investigations****
- ✓ **Appropriate therapy**

Clinical Manifestations

- ❖ **Meningitis**
 - predominantly involves the subarachnoid space
 - ✓ Encephalitis
 - generalized or focal involvement of brain parenchyma
 - cerebritis or abscess (depending on the formation of capsule)
- ❖ **Presentations**
 - Fever, headache, meningismus, and altered mental status
 - Acute meningitis
 - A few hours to several days
 - Vary depending on the microorganism
 - Virus, bacteria, parasites
 - Subacute or chronic meningitis
 - Over weeks to months
 - More gradual onset and lower fever
 - Mycobacteria, spirochetes, fungus
 - depending on the host immune status
 - ex. Cryptococcal meningitis in AIDS and non-AIDS patients

Clinical Manifestations

❖ Encephalitis

Share the triad of fever, headache, and altered mental status

Cerebral cortex involvement

Mental status change (confusion)

behavioral and speech disturbances

focal neurologic signs (seizures, hemiparesis)

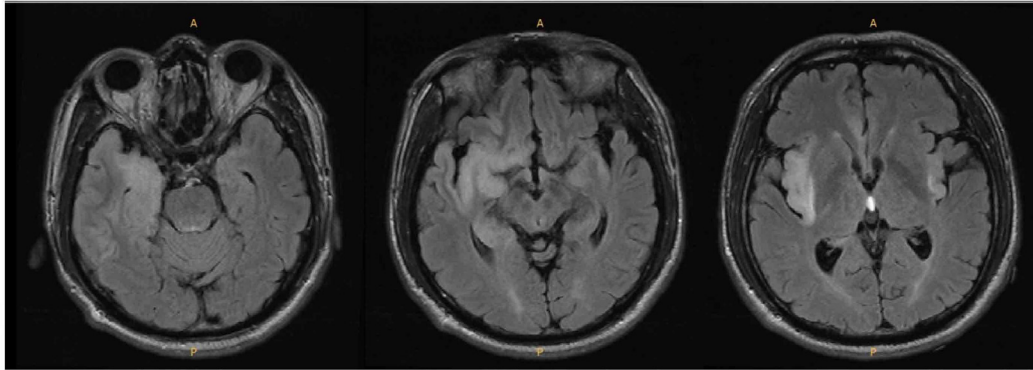
❖ Etiologies

- Virus: HSV, other herpesviruses, enterovirus, flavivirus...
- Non-viral: *L. monocytogenes*, Rickettsia, Toxoplasma...
 - Neuroimaging findings (HSV vs. JE)
 - Temporal associations
 - other information
 - geographic locale and prevalence of disease
 - occupation, travel history, recreational activities
 - immune status and vaccination history
- Non-infectious
 - ADEM, anti-NMDAR encephalitis

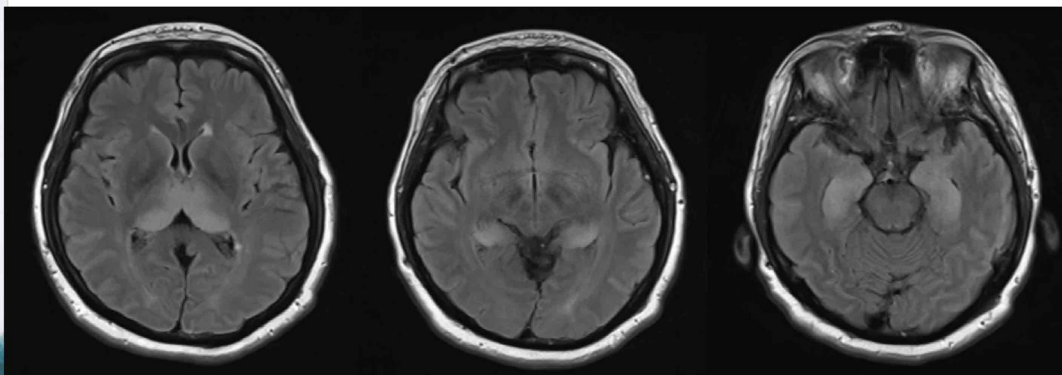
Differential diagnosis

Features	Viral encephalitis	Autoimmune	Encephalopathy
Onset	Acute-subacute	Acute-subacute-chronic	Subacute
Fever	Common	Occasional	Uncommon
Depressed mental status	Fluctuate, progression	Fluctuate, progression	Steady decline
Focal neurologic signs	Common	Frequently limbic	Uncommon
Seizures (type)	Common (generalized or focal)	Common (generalized or focal)	Uncommon (generalized)
CSF profile	Moderate lymphocytic pleocytosis, mild protein elevation	Mild lymphocytic pleocytosis, mild protein elevation	Normal
EEG	Diffuse slowing and focal changes	Temporal slowing and sharp waves	Diffuse slowing
MRI pattern	More confluent, gray and white matter; rarely, deep nuclei	Mesial temporal T2 hyperintensity	Normal

M/63 HSV encephalitis



F/50 Japanese encephalitis



CSF study

- ❖ Essential procedure in the diagnosis of meningoencephalitis

Routine tests	Specific tests
WBC count with differential	Viral PCR
RBC count	AFB, TB-PCR
Glucose	VDRL (RPR), FTA-ABS
Protein	India ink, fungus culture
Gram stain and culture	Cryptococcal Ag
	Cytology
	Antibody test (IgG and IgM)*
	Neuronal autoantibodies*

CSF study

- ❖ **Opening pressure**
Normal range: 50 to 195 mm H₂O
- ❖ **Appearance**
Clear and colorless
Turbid
increased WBC (> 200/mm³), bacteria (> 10⁵ CFU/mL)
Xanthochromia
yellow-orange supernatant of centrifuged CSF
RBC lysis (after 2-4 hr), CSF protein (> 150 mg/dL)
hyperbilirubinemia (> 10 - 15 mg/dL).
- ❖ **Cell count**
[Blood contamination]
Adjusted WBC count = CSF WBC – CSF RBC * (Blood WBC / Blood RBC)

Typical CSF findings

Cause	WBC (/mm ³)	Cell type	Glucose (mg/dL)	Protein [§] (mg/dL)
Viral	10 – 500	Mononuclear*	> 45 [†]	< 200
Bacterial	1,000 – 5,000	Neutrophilic	< 40	100 – 500
Tuberculosis	50 – 300	Mononuclear	< 45	50 – 300
Cryptococcal	20 - 500	Mononuclear [‡]	< 40	> 45

*May be neutrophilic pleocytosis early in presentation

HSV and Enterovirus (shift to lymphocyte), WNV, CMV (persistent PMN)

[†] Low CSF glucose

Mumps, LCM virus (moderate), HSV, VZV (mild)

[‡] 75% of patients with AIDS have < 20 cells/mm³

[§] subtracting 1 mg/dL of protein for every 1,000 RBC/mm³

CSF Tests

- Gram stain
 - positive in 60% to 90% of acute bacterial meningitis
 - Bacterial culture positive in 70 – 85%
- AFB smear
 - positive 15% to 25% of specimens of tuberculous meningitis
- No effective specialized stains
 - Spirochetal (*T. pallidum* or *B. burgdorferi*) meningitis
 - Toxoplasma* encephalitis
 - : serum or CSF antibody studies in the diagnosis
- CSF India ink
 - positive in 50% to 75% of cryptococcal meningitis
 - (increases to 88% in patients with AIDS)

CSF Tests

• CSF PCR tests

highly sensitive and specific for the diagnosis of CNS infection

❖ Viral PCR

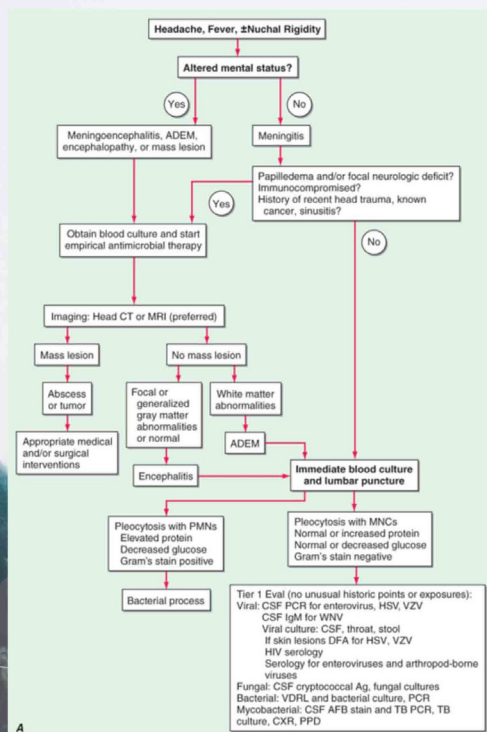
HSV encephalitis: 96 - 98% sensitive, 95 - 99% specific in adults
Repeat HSV PCR 3 to 7 days later (initially negative, but suspected)
CMV, Enterovirus, VZV, JC virus

❖ bacterial meningitis

Bacterial PCR panel: 100% sensitive, 98% specific
Negative predictive value 100% → useful in exclusion diagnosis

❖ Tuberculous meningitis

TB-PCR sensitivity 60 – 90 %
→ Negative PCR cannot exclude TB meningitis



Tier 1 tests (additional)

Viral PCR (HSV 1/2, VZV, EBV, CMV, enterovirus, HHV6)

Respiratory virus PCR panel (sputum)

Influenza virus A/B Ag (swab)

CSF Bacterial Ag panel (latex agglut.)

CSF Bacterial PCR panel

Legionella Ag

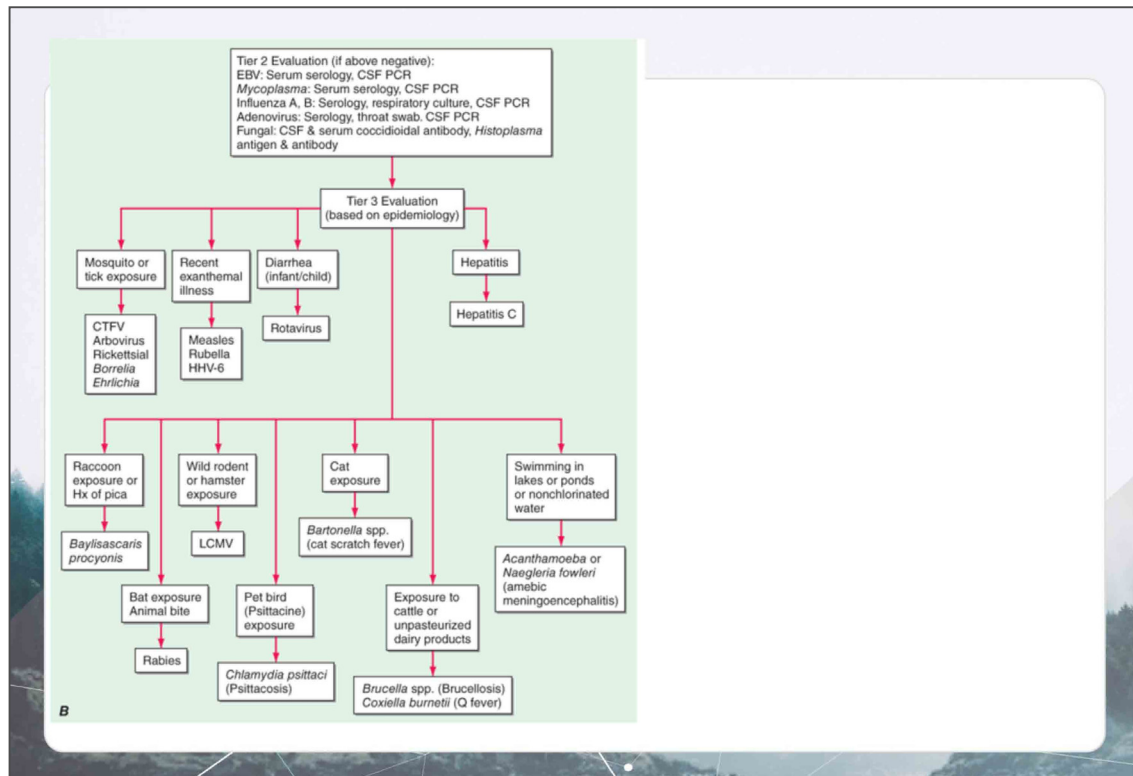
O. tsutsugamushi Ab

Mycoplasma IgM/IgG, Leptospira Ab

Aspergillus Ag

*Japanese encephalitis Ab (summer, fall)

*Neuronal autoantibodies



Possible Etiologic Agents of Encephalitis

Risk factor	Possible infectious agents
Mosquitoes	JEV, WNV, <i>P. falciparum</i> (DENV, Chikungunya, Zika virus)
Ticks	Tick-borne encephalitis, Lyme, (Scrub typhus, SFTS)
Late summer/early fall	All agents transmitted by mosquitoes and ticks Enterovirus
Camping/hunting	All agents transmitted by mosquitoes and ticks
Winter	Influenza virus; LCMV
Exposure to Cattle Unpasteurized milk	Brucellosis, Q-fever (<i>C. burnetii</i>)
Unvaccinated	JEV; VZV; poliovirus; measles; mumps; rubella virus
Immunocompromised	VZV; CMV; HHV-6; WNV; HIV; JC virus; <i>T. gondii</i> ; <i>L. monocytogenes</i> ; <i>M. tuberculosis</i> ; <i>C. neoformans</i>
Recent vaccination	ADEM

Cause of specific encephalitis syndromes

Limbic encephalitis	Cerebellitis	Parkinsonism	Rhombencephalitis*	Encephalomyelitis**
HSV	VZV	JEV	<i>Listeria</i>	JEV (WNV)
NMDAR Ab	EBV	WNV	JEV (WNV)	Enterovirus-71
VGKC Ab	Paraneoplastic	St. Louis	Enterovirus-71	Tick-borne encephalitis
HHV-6	<i>Brucella</i>	Nipah virus	<i>Brucella</i>	Poliovirus
<i>T. pallidum</i>	Mumps		Paraneoplastic	Rabies
	Whipple		NMO	

*brainstem involvement

**accompanied by acute flaccid paralysis (polio-like)

Chronic and recurrent meningitis

Chronic inflammation of the meninges (pia, arachnoid, and dura)
 neurologic syndrome exists for >4 weeks
 associated with persistent inflammatory response in CSF (WBC > 5 /uL)

Five categories of disease

- (1) Meningeal infections
- (2) Malignancy
- (3) Autoimmune inflammatory disorders
- (4) Chemical meningitis
- (5) Parameningeal infections

Symptoms and Signs of Chronic Meningitis

Symptom	Sign
Chronic headache	± Papilledema
Neck or back pain/stiffness	Brudzinski's or Kernig's sign
Change in personality	drowsiness, inattention, disorientation, memory loss, frontal release signs
Facial weakness	Peripheral seventh CN paresis
Double vision	Paresis of CNs III, IV, VI
Hearing loss	CN VIII paresis
Arm or leg weakness	Myelopathy or radiculopathy Frontal lobe dysfunction (hydrocephalus)
Numbness in arms or legs	
Urinary retention/incontinence	

Infectious Causes of Chronic Meningitis

Bacterial (common)	Viral
Partially treated meningitis	Mumps
Parameningeal infection	Lymphocytic choriomeningitis (LCMV)
<i>Mycobacterium tuberculosis</i>	Echovirus
<i>Borrelia burgdorferi</i> (Lyme disease)	HIV (acute retroviral syndrome)
Syphilis (<i>Treponema pallidum</i>)	HSV (recurrent, type 2)
Fungal	Protozoal and Helminthic
<i>Cryptococcus neoformans</i>	<i>Toxoplasma gondii</i>
<i>Candida</i> sp.	Cysticercosis
<i>Histoplasma capsulatum</i>	<i>Gnathostoma spinigerum</i>
<i>Coccidioides immitis</i>	<i>Angiostrongylus cantonensis</i>
<i>Aspergillus</i> sp.	<i>Baylisascaris procyonis</i>

Noninfectious Causes of Chronic Meningitis

Causes	Risk factors
Malignancy	Metastatic cancer of breast, lung, stomach, or pancreas; melanoma, lymphoma
Sarcoidosis	CN palsy, enlarged lymph node, peripheral neuropathy
Vogt-Koyanagi-Harada syndrome	Recurrent meningoencephalitis with uveitis, retinal detachment
Systemic lupus erythematosus	Encephalopathy; seizures; stroke; transverse myelopathy; rash; arthritis
Behçet's syndrome	Oral and genital aphthous ulcers; iridocyclitis
Mollaret's meningitis	HSV-2; rare cases due to HSV-1
Granulomatosis with polyangiitis (Wegener's)	Associated sinus, pulmonary, or renal lesions; CN palsies
IgG4-Related Hypertrophic Pachymeningitis	storiform fibrosis with plasma cell infiltration, increased IgG4 in serum and CSF

Summary

- Differential diagnosis
 - Clinical syndromes
 - Autoimmune encephalitis
 - Epidemiological characteristics for infectious agents
 - CSF profiles and MRI findings
- Thorough laboratory investigations
 - Initial study (before antimicrobial treatment)
 - PCR results: highly sensitive and specific
 - Appropriate serological evaluation if necessary