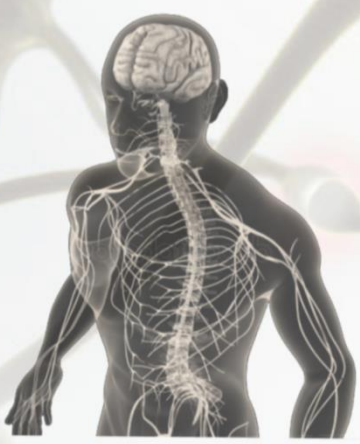
Central Nervous System

Sheet 4



Subject | Micro

Done by | Yousef Omar

Correction | ...

Doctor | Anas

***Let's start with viral meningitis :

-Viral meningitis is different than bacterial meningitis in terms of: Immune response. So, after taking a lumber puncture, there would be different type of cells, glucose and protein level in CSF.

-Viral meningitis is also called aseptic meningitis (Aseptic>>> No bacteria)

-Symptoms of viral meningitis are less severe than acute bacterial meningitis.

-Viral meningitis has similar symptoms to bacterial meningitis (head ache, fever, and signs of meningeal irritation), but rarely produces **focal neurological defects** and profound alterations in conciousness.

Note: Focal neurological deficits: Include any deficit caused by focus of infection or damage in the brain. **E.g.** Mass effecting a cranial nerve responsible for eye muscles causing diplopia. Also damage of certain fibers in Rt. side causing hemipersis on the opposite side. Also Hearing loss due to damage of certain area of the brain.

-Enteroviruses are the leading cause of viral meningitis, e.g. echoviruses, Coxsackie viruses, Polio viruses, enteroviruses 70 and 71.

Note: Enteroviruses are named so, because they are transmitted through GIT (feco-orally). Remember that they don't cause GIT infection/symptoms.

Note: Polio virus is ingested, then primary replication occur in the intestine, then it reach the blood, then it reach nerves>> damaging them.

-Other causes: Varicella-zoster virus and herpes simplex virus 2, Epstein barr virus, arthropod-borne virus and HIV.

Acute Meningitis	
Common	Less Common
Enteroviruses (coxsackieviruses, echoviruses, and human enteroviruses 68–71) Varicella-zoster virus Herpes simplex virus 2 Epstein-Barr virus Arthropod-borne viruses HIV	Herpes simplex virus 1 Human herpesvirus 6 Cytomegalovirus Lymphocytic choriomeningitis virus Mumps

***Note: HSV can cause encephalitis, more commonly with HSV type 1, whereas viral meningitis is caused by HSV type 2.

***Note: Arthropod -borne viruses, are a common cause of outbreaks of encephalitis. They can also cause meningitis.

-Incidence is not clear but seasonal variations are found especially in temperate climates . (In temperate climates, there is a substantial increase in cases during the nonwinter months).

-susceptible groups to viral meningitis are often children and neonates. Remember in this case they don't give the typical representation of meningitis of Headache, fever and meningeal signs , So in there would be non-specific symptoms.

***Specific viral presentations:

- Enterovirus: in neonates, fever is accompaniedby vomiting, anorexia, rash, and upper respiratory tract symptoms (Non-specfic symptoms), also you would find neck stiffness which is an important clue for meningitis, so if you move his head, it causes the child to cry more. In older children and adults, symptoms are milder with fever, headache, neck stiffness, and photophobia .
- Mumps virus: it cases decreased due to vaccines. If there is parotitis (swelling of parotid gland), you suspect Mumps virus. CNS symptoms usually occur 5 days after the onset of parotitis.
- VZV meningitis is associated with a characteristic, diffuse vesicular rash (petechial rash).

If a child come to clinic with diffuse petechial rash and signs of meningitis, then you suspect N. meningitidis since it cause meningococcemia which represent as petechial rash, then it crosses BBB to cause meningitis. BUT in the case of VZV, first it causes chicken pox, then it spends its latency period in sensory neurons in dorsal ganglia, then reactivation occur in the form of shingles, and if its accompanied by a diffuse vesicular rash and meningeal signs then suspect VZV meningitis.

- HSV-2 meningitis presents with classical symptoms, that might be associated with a history of genital herpes.

Bacterial meningitis cause depends mainly on the age of patient and immune status but in case of viral meningitis cause depends on associated symptoms. But in general to diagnose meningitis then take lumber puncture.

***How to confirm a diagnosis of viral meningitis?

- CSF examination and viral culture are important.
- PCR to look for the genetic material of virus, which is the single most important test to diagnose CNS viral infection.
- Serology: to look for antibodies against enteroviruses, for example IgM indicate recent infection with enterovirus.

***The table below indicate CSF lab test results:

- ✓ In bacterial meningitis there is predominance of PMNs,while in viral/fungal/tubercular meningitis there is predominance of Lymphocytes.
- ✓ WBC count increases in all cases, but mostly in bacterial meningitis
- ✓ Protein level can be normal to elevated and CSF to serum glucose ratio is normal in case of viral meningitis. But in case of bacterial meningitis, protein is elevated and glucose is markedly decreased.
- ✓ Type of cells, protein and glucose can help in differential diagnosis of meningitis, in addition to history and accompanied symptoms.
- ✓ In viral meningitis: gram stain and culture are negative, normal glucose and protein with neutrophils and lymphocytes (Presence of neutrophil indicate viral meningitis in early stages)

Test	*Bacterial*	*Viral*	*Fungal*	*Tubercular*
Opening pressure	Elevated	Usually normal	Variable	Variable
White blood cell count	≥1,000 per mm³	<100 per mm³	Variable	Variable
Cell differential	Predominance of PMNs*	Predominance of lymphocytes†	Predominance of lymphocytes	Predominance of lymphocytes
Protein	Mild to marked elevation	Normal to elevated	Elevated	Elevated
CSF-to-serum glucose ratio	Normal to marked decrease	Usually normal	Low	Low

***How to manage viral meningitis?

- ❖ Remember that treatment is different than bacterial meningitis, but in case you have a case of meningitis that you aren't sure whether its viral or bacterial, then give 3rd generation cephalosporin (Cefotrixone/Cefotaxime), which it has a wide spectrum that cover most of suspected organisms.
- ❖ If the case is confirmed to be viral after release of results of CSF/PCR:

In case its due to herpes>>> give Acyclovir. Otherwise give supportive treatment for pain (analgesics), fever (antipyretic), vomiting/diarrhea (antiemetic). Fluid and electrolyte status should be monitored.

- ❖ Prognosis is better than bacterial meningitis.

Remember in bacterial meningitis, even if treatment is started early on, still there is risk of sequalae especially in children leading to cognitive retardation, hearing loss, etc. But in case of viral meningitis recovery is better, but still there are some cases of sequalae but to much lesser extent than bacterial meningitis.

- ❖ In adults, the prognosis for full recovery from viral meningitis is excellent.
- ❖ The outcome in infants and neonates (<1 year) is less certain; intellectual impairment, learning disabilities, hearing loss, and other lasting sequelae have been reported in some studies.

***Case Study:

Case Study and Questions

A 6-year-old girl was brought to the doctor's office at 4:30 PM because she had a sore throat, had been unusually tired, and was napping excessively. Her temperature was 39° C. She had a sore throat, enlarged tonsils, and a faint rash on her back. At 10:30 PM, the patient's mother reported that the child had vomited three times, continued to nap excessively, and complained of a headache when awake. The doctor examined the child at 11:30 PM and noted that she was lethargic and aroused only when her head was turned, complaining that her back hurt. Her CSF contained no red blood cells, but there were 28 white blood cells/mm^3—half polymorphonuclear neutrophils and half lymphocytes. The glucose and protein levels in the CSF were normal, and Gram stain of a specimen of CSF showed no bacteria.

1. *What were the key signs and symptoms in this case?*
2. *What was the differential diagnosis?*
3. *What signs and symptoms suggested an enterovirus infection?*
4. *How would the diagnosis be confirmed?*
5. *What were the most likely sources and means of infection?*
6. *What were the target tissue and mechanism of pathogenesis?*

Answers

1. The key signs and symptoms were sore throat, fever, faint rash, excessive napping, lethargy, headache, and pain upon turning head (stiff neck). The presence of lymphocytes in the CSF and normal glucose and protein levels minimizes the diagnosis of a bacterial infection.
2. The differential diagnosis is aseptic meningitis that is likely caused by a virus such as an enterovirus, HSV, or lymphocytochoriomeningitis virus, or by an arboencephalitis virus from the Togaviridae, Flaviviridae, or Bunyaviridae families. *Cryptococcus neoformans* (fungus), *Mycobacterium tuberculosis*, and *Borrelia burgdorferi* are also possible. However, the presence of a rash and sore throat before signs of meningitis strengthen the likelihood of an enterovirus infection, such as coxsackievirus A or echovirus. At an earlier time (30 years ago), polio would also be in the differential diagnosis.
3. The rash and sore throat in the prodrome period and the presence of lymphocytes in the CSF distinguish an enterovirus meningitis from other microbial causes.
4. An RT-PCR analysis would identify the enterovirus in the CSF and confirm the diagnosis.
5. Enteroviruses are spread by the fecal-oral and aerosol routes.
6. The initial target tissues for enteroviruses are the mucoepithelium, lymphoid tissue of the tonsils and pharynx, and Peyer patches of the intestinal mucosa. The virus is cytolytic.

The case indicate a 6 years old girl that was brought ot the clinic due to sore throat, usually tired, napping excessively with high temperature, enlarged tonsils and faint rash on the back, so she have non-specific symptoms. Then after 6 hours (at 10:30pm), she started vomiting with decreased level of consciousness causing her to nap excessively . And complained of headache when awake. These symptoms make you suspicious of meningitis. The doctor examined her 11:30pm and noted that she was lethargic and aroused only when her head was turned (due to neck stiffness) , complaining that her back hurt. Her CSF contained no RBC but there were 28 WBC cells/mm^3 (half neutrophil and half lymphocyte>>viral meningitis). Glucose and protein levels are normal in CSF. Negative gram stain. Vomiting and sore throat suggest enterovirus infection.

Cryptococcus neoformans(fungal) and mycobacterium TB is added to differential diagnosis due to presence of lymphocytes. They are found less in cases of acute meningitis, and mainly present in chronic meningitis causing headache for more than 4weeks.

End of viral meningitis

***Now let's start with Brain abscess:

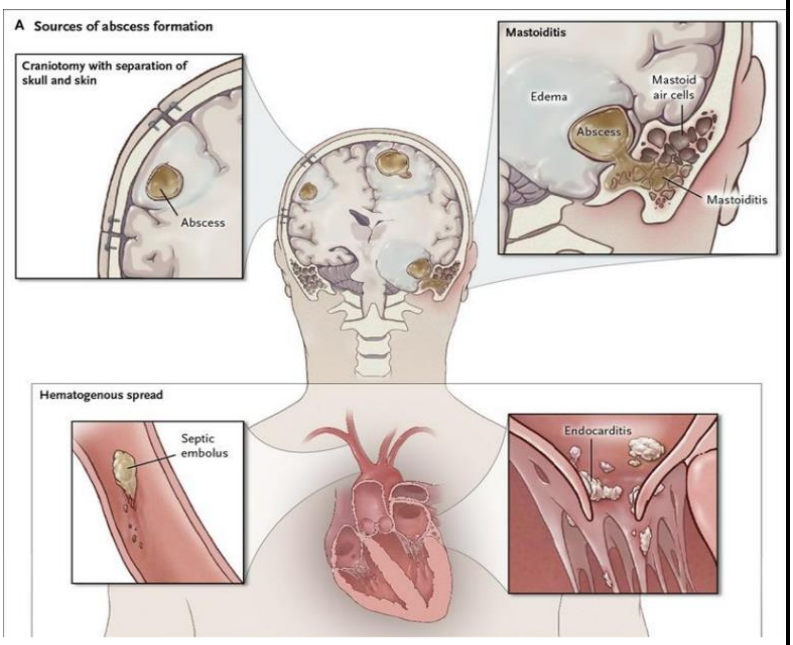
-It's a space occupying lesion enclosed in a certain part of brain. But in case of meningitis/encephalitis its generalized, so meninges from brain down to spinal cord gets inflamed.

-A brain abscess is a focal, suppurative infection within the brain parenchyma, typically surrounded by a vascularized capsule.

-Cerebritis, which is a similar lesion with no capsule, and sometimes precedes abscess formation. So, bacteria enter brain parenchyma causing destruction of tissue around it, at this level its called cerebritis, then it starts to form a capsule around damaged area forming abscess which contain pus, neutrophils, bacteria, etc.

-Brain abscess formation is rare in immunocompetent adults less than 1 in 100000 person per year, so mostly it effects immunocompromised or trauma.

***Sources of Brain abscess:



>>>Pathogen can spread from nearby ear, sinus, and dental infections, through blood vessels, or directly as in head trauma.

>>>Following neurological procedures (craniotomy), like for example patient with trauma and bleeding in meningies came to emergency and a craniotomy was performed. After a while this patient came again due to focal neurological symptoms like inability of moving his hand, hearing loss,… which most probably is due to bacterial invasion during craniotomy mostly staph. aures.

>>>Infection in nearby structure like mastoiditis , sinusitis or otitis media, which increase risk for brain abscess and meningitis.

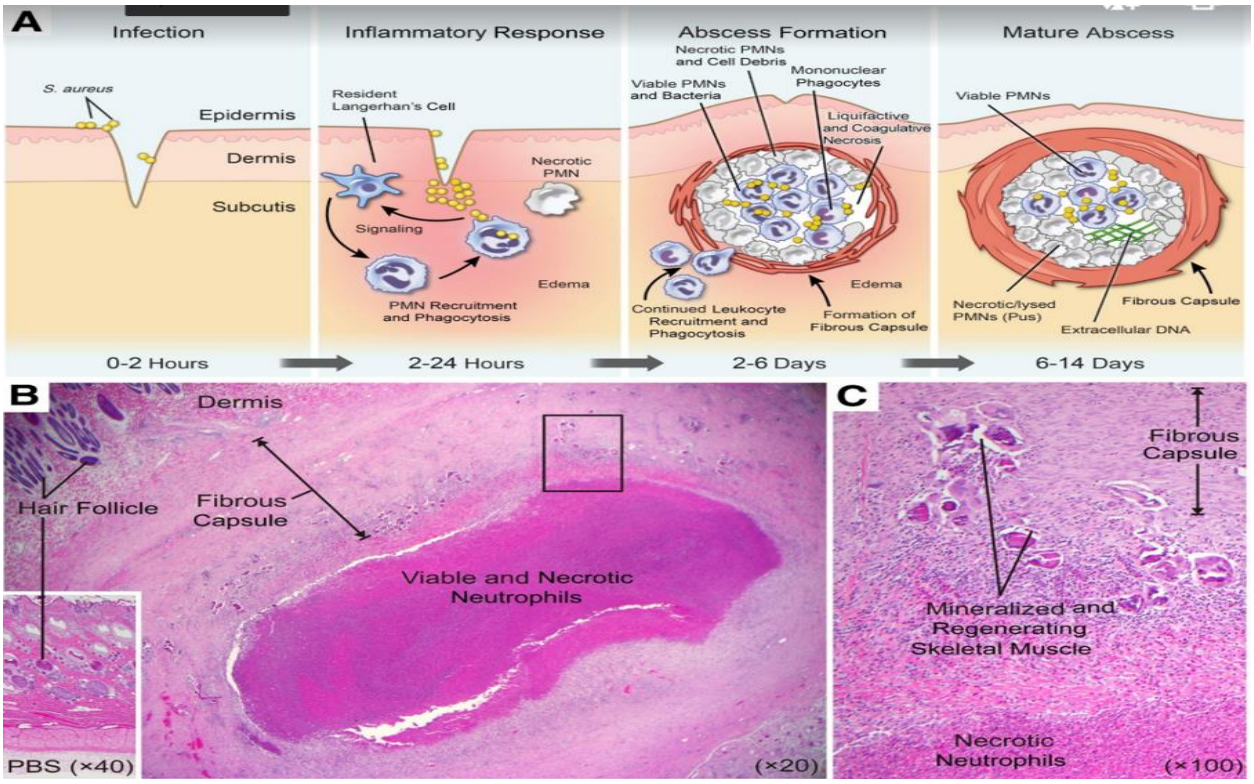
>>>Hematogenous spread, some bacteria (staph or strep.) may adhere to abnormal valves forming an infection focus, which then is dislodged reaching blood, then it can reach brain and crosses BBB casuing brain abscess. For Example Endocarditis or septic embolus.

***How are abscesses formed?

-Abscesses may occur in any kind of tissue, and are the result of the immune response to invading pathogens.

>>>Bacteria enter the parenchyma of the brain, then cells recognize bacteria and start to secrete cytokines (IL-1 and TNF-α), to recruit neutrophils mostly which secrete more cytokines, antimicrobial peptide and reactive oxygen and nitrogen species in order to eliminate the

bacteria, but at the same time it damage the tissue, also PMNs start to die due to short life span. And during this process capsule fibers are formed to seal off the abscess enclosing the the damaged area. This capsule is composed of filled with live and dead bacteria, white blood cells, and cell debris. This figure is taken from the skin but the the process is the same in any part of the body.



***What are the common causative agents?

-The organism usually depends on the primary focus of infection.

-From nearby structures, like otitis media/mastoidits, sinusitis and dental procedure>>Streptococci , bacteroides and hameophilus

-Following head trauma and neurosurgery>>staph aureus and staph spp. in general.

-In immunocompromised>> L. monocytogenes, parasites ,Nocardia spp. and fungi

Note: Parasites include toxoplasma gondii which causes a self limited infection, and its definite host is cats. In immunocompetent patient it doesn't cause any disease but causes disease in pregnant women and immunocompromised. Its an intriguing pathogen, since some studies suggest that when toxoplasma gondii is transmitted to mouse, it become less avert to cat urine.

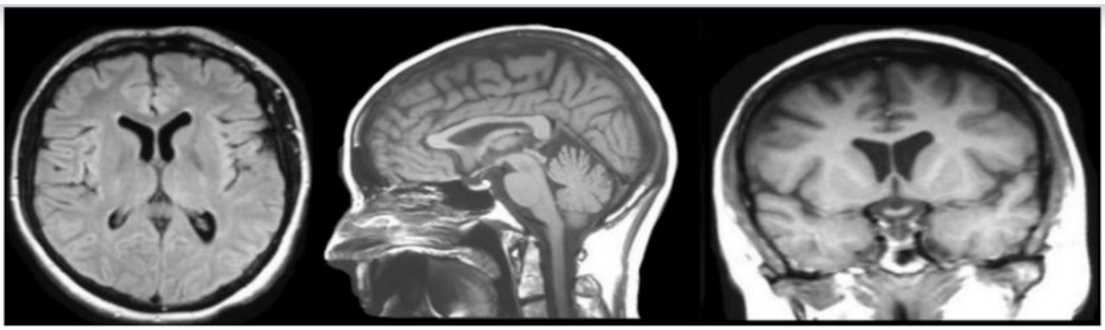
Table 19.10 Factors predisposing to cerebral abscess

Predisposing condition	Microorganisms
Otitis media/mastoiditis	Streptococci, *Enterobacteriaceae*, *Bacteroides* spp., *P. aeruginosa*
Sinusitis	Streptococci, *Haemophilus* spp., *Bacteroides* spp., *Fusobacterium* spp.
Dental sepsis	Streptococci, *Haemophilus* spp., *Bacteroides* spp., *Fusobacterium*, *Prevotella*
Pulmonary/pleural sepsis	Streptococci, *Fusobacterium*, *Actinomyces*, *Bacteroides*, *Prevotella* spp., *Nocardia* spp.
Endocarditis	*S. aureus*, streptococci
Congenital heart disease	Streptococci, *Haemophilus* spp.
Urinary tract	*Enterobacteriaceae*, *P. aeruginosa*
Head trauma	*S. aureus*, *Enterobacter* spp., *Clostridium* spp.
Neurosurgery	*Staphylococcus* spp., *Streptococcus* spp., *P. aeruginosa*, *Enterobacter* spp.
Immunocompromised hosts	*T. gondii*, *L. monocytogenes*, *N. asteroides*, *Aspergillus*, *C. neoformans*, *C. immitis*, *Candida* spp., mucormycosis, zygomycosis
HIV infection	*T. gondii*, *Nocardia* spp., *Mycobacterium* spp., *L. monocytogenes*, *C. neoformans*

-In case of long standing UTI (upper tract infection) in immunocompromised patient>> Enterobacteriaceae (E. coli)

***How do patients present?

- Headache, fever, seizures, and focal neurological signs are common which depend on its location. Through brain imaging(MRI) , you can identify the location of lesion. Figure below indicate pneumococcal brain abscess



Normal brain MRI

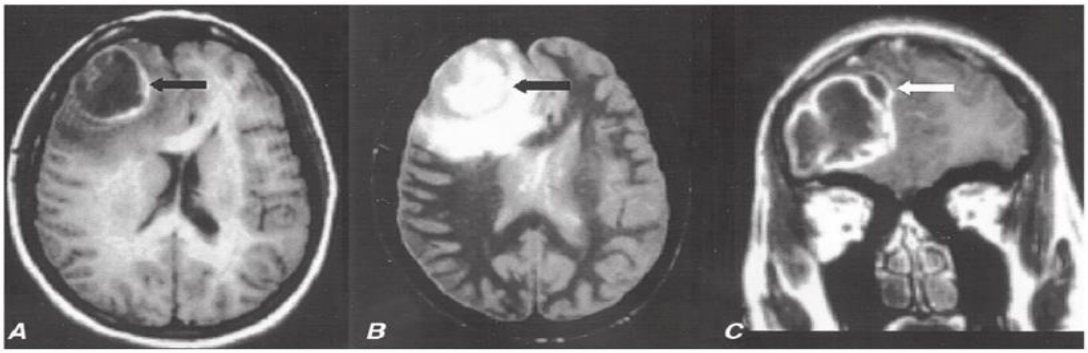


FIGURE 36-4
Pneumococcal brain abscess. Note that the abscess wall has hyperintense signal on the axial T1-weighted magnetic resonance imaging (MRI) (A, black arrow), has hypointense signal on the axial proton density images (B, black arrow), and enhances prominently after gadolinium administration on the coronal T1-weighted image (C). The abscess is surrounded by a large amount of vasogenic edema and has a small "daughter" abscess (C, white arrow). (Courtesy of Joseph Iurito, MD; with permission.)

- Brain imaging (MRI, CT scan with contrast) should be performed urgently to confirm the diagnosis. Remember its not important in case of meningitis.

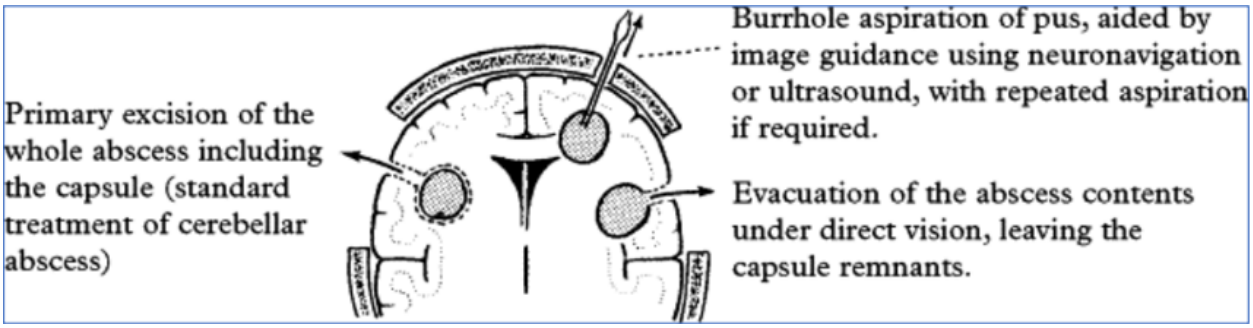
-Since it's a space occupying lesion, it cause increased intracranial pressure>>> so taking lumber puncture is contraindicated and dangerous since it would cause brain herniation. So confirm the abscess with MRI or positive blood cultures(10%) (due to hematogenous spread).

***How to manage brain abscess ?

>>>perform a neurosurgical drainage of the abscess, and you must remove all of it even with capsule to prevent recurrence. Drainage of the abscess is usually necessary along with taking a swap for culture and cytology of the suppuration to identify the pathogen and do sensitivity testing and depending on test results you will give specific antibiotics.

In brain abscess there will be sequalae, because during removal of abscess it will damage part of brain tissue and depends on lesion location.

Empiric therapy with 3rd generation cephalosporin can be started, in addition to antibiotics depending on suspicion. (e.g. History of recent head trauma increases chances of S. aureus, and Vancomycin can be added). Remember we take a swab and perform a culture to identify the pathogen then perform sensitivity testing then give directed antibiotic therapy.



***Follow up and prognosis of brain abscess:

-To make sure that infection won't recur, serial MRI and CT scans should be obtained on a monthly or twice-monthly basis to document resolution of the abscess.

-Mortality is less than 15%, But a significant sequalae occur including seizures, persisting weakness, aphasia, or mental impairment, occur in 20% of survivors depending on location of lesion.

-Enhanced neuroimaging techniques, improved neurosurgical procedures, and improved antibiotics helped decrease mortality.

END of brain abscess

***Now let's start with another space occupying lesion called subdural empyema:

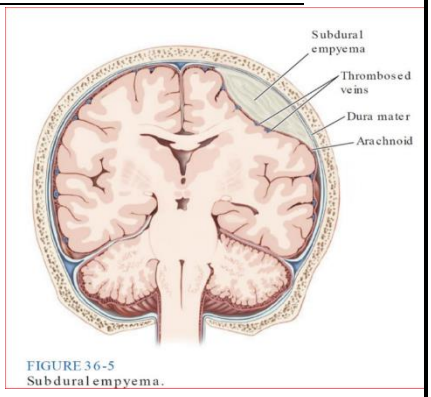


FIGURE 36-5
Subdural empyema.

- A subdural empyema (SDE) is a collection of pus between the dura and arachnoid membranes.

-Remember that subdural space is a virtual small slit-like space that has little amount of fluid, but in case of infection, pus accumulate in this space. The evolution of SDE can be extremely rapid because the subdural space is a large compartment that offers few mechanical barriers to the spread of infection.

- Pathogens, pathophysiology, and clinical presentation in SDE is similar to a brain abcsess, and other infectious space occupying lesions But SDE have a more rapid represention.

- SDE is a rare disorder that accounts for 15–25% of focal suppurative CNS infections. With a striking predilection for young males.

- Aerobic and anaerobic streptococci, staphylococci, Enterobacteriaceae, and anaerobic bacteria are the most common causative organisms of sinusitis-associated SDE. (from slides)

- A patient with SDE typically presents with fever and a progressively worsening headache, Presence of underlying sinusitis should raise suspicion of SDE. (from slides)

- Contralateral hemiparesis or hemiplegia is the most common focal neurologic deficit and can occur from the direct effects of the SDE on the cortex or as a consequence of venous infarction. (from slides)

***How to diagnose subdural empyema?

>>>Perform brain imaging (MRI is usually used). MRI is superior to CT in identifying SDE and any associated intracranial infections.

>>>CSF examination should be avoided due to increased intracranial pressure, since accumulation of pus occur rapidly so ICP increases rapidly. Also CSF adds no useful information.

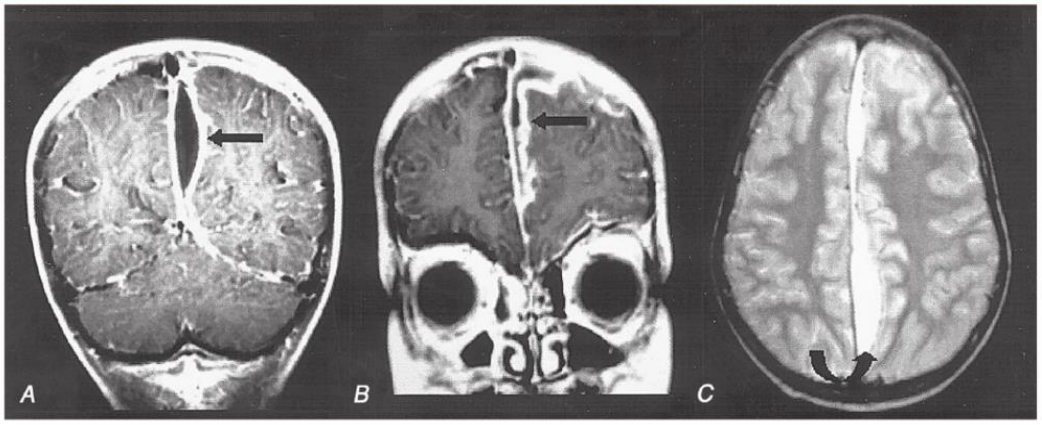


FIGURE 36-6
Subdural empyema. There is marked enhancement of the dura and leptomeninges (A, B, straight arrows) along the left medial hemisphere. The pus is hypointense on T1-weighted images (A, B) but markedly hyperintense on the proton density–weighted (C, curved arrow) image. (Courtesy of Joseph Iurito, MD; with permission.)

*** How to treat subdural empyema (SDE)?

- SDE is a medical emergency. Emergent neurosurgical evacuation of the empyema, either through craniotomy, craniectomy, or burrhole drainage is the definitive step in the management of this infection and to relieve the pressure

- Empiric antibiotic therapy should include a 3rd generation cephalosporin, vancomycin and metronidazole. (again depending on suspicion from patient's history).

- Specific diagnosis of the etiologic organisms is made based on Gram's stain and culture of fluid obtained via either burr holes or craniotomy, based on test results give directed therapy.

END of subdural empyema

***Now let's start with Epidural abscess:

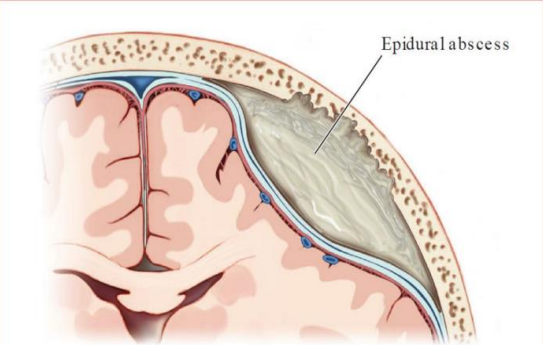


FIGURE 36-7
Cranial epidural abscess is a collection of pus between the dura and the inner table of the skull.

- Cranial epidural abscess(NOT empyema) is a suppurative infection occurring in the potential space between the inner skull table and dura.

- Note that dura are tightly adherent to the skull, so an epidural abscess spreads slower than SDE, and is usually smaller in size. Moreover, focal neurological deficits are uncommon (5% of patients).

- Similar routes of infection to other suppurative space occupying infections (but more commonly encountered after craniotomy procedures and cranial fractures. And rarely hematogenous).

- Presentation, diagnosis, Causative agents (and hence empiric treatment) are similar to SDE but it has less severe representation than SDE.

END of Epidural abscess

***Following these focal neurological lesions with inflammation, **Suppurative intracranial thrombophlebitis** may occur in veins, damaging them and that lead to increased risk of thrombus formation and inflammation.

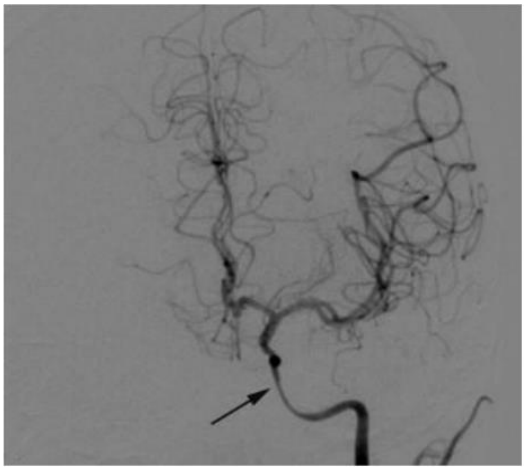
Suppurative intracranial thrombophlebitis is septic venous thrombosis of cortical veins and sinuses.

Note: Thrombophlebitisis a phlebitis (inflammation of a vein) related to a thrombus (blood clot)

Commonly a complication of other CNS infections like bacterial meningitis; SDE; and epidural abscess or related to skin infections on the face.

Veins draining infected meninges or sinuses can be damaged by the suppuration followed by clotting of those veins. Thrombosis may extend from one sinus to another, and at autopsy, thrombosis of different histologic ages can be detected in several sinuses

*** How is Suppurative intracranial thrombophlebitis diagnosed and treated ?



- MRI can show decreased blood flow in the affected veins.

- Septic venous sinus thrombosis is treated with antibiotics, hydration, and removal of infected tissue and thrombus. Anticoagulation with dose-adjusted intravenous heparin is sometimes recommended.