Case Studies: Introduction to Central Nervous System Infections

Infections of the central nervous system (CNS) are infrequent compared to the other infections discussed for other organ systems of the human body, but they are very important because of the high mortality rates and the serious sequelae associated with them, including learning, speech, and motor skills disorders, seizures, and hearing and sight loss. The most frequent CNS infections are meningitis, encephalitis, and abscess. Intoxication with tetanus and botulinum toxins can affect the CNS, causing spastic or flaccid paralysis, but these diseases are quite rare in the developed world.

There are two major forms of meningitis, septic and aseptic. Septic meningitis is typically caused by bacteria. The cerebrospinal fluid (CSF) is usually cloudy, with over 1,000 white blood cells per μl with neutrophils predominating; increased protein levels due to inflammation; and decreased glucose due in part to metabolism by white blood cells. Aseptic meningitis can be caused by viruses, fungi, or *Mycobacterium tuberculosis*. In aseptic meningitis, the CSF is "clear" due to a cell count typically in the 100-500/μl range. Except very early in the disease course, the predominant cell type is mononuclear, with lymphocytes predominating. CSF glucose levels are frequently normal, but they may be decreased in over half of patients with fungal or mycobacterial infections. CSF protein levels are frequently normal except with *M. tuberculosis*, where they are typically elevated.

Bacterial meningitis is most common in the very young, the very old, and the immunocompromised; of these, it is seen most commonly in children 2 months to 5 years of age. Group B streptococci are the most common cause of neonatal meningitis (newborns to 2 months). *Listeria monocytogenes* is another organism that causes neonatal disease. It also is an important agent of meningitis in the immunosuppressed. Gram-negative enteric bacilli, including *Escherichia coli*, *Klebsiella pneumoniae*, and *Citrobacter diversus*, may also cause neonatal meningitis. Congenital syphilis, which may manifest itself during the neonatal period, frequently will have a CNS component, neurosyphilis. Until recently, *Haemophilus influenzae* type b was the most common cause of bacterial meningitis in children 2 months to 5 years of age, but the widespread use of conjugated *H. influenzae* type b vaccine has resulted in a dramatic decline in the incidence of this disease. *Streptococcus pneumoniae* and *Neisseria meningitidis* are now the leading causes of meningitis in this age group and the elderly.
Individuals with head trauma are also at risk for developing bacterial meningitis. The organisms most frequently associated with this type of bacterial meningitis are coagulase-negative staphylococci (especially in patients with CNS shunts or who have undergone neurosurgical procedures), *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. *M. tuberculosis* meningitis is seen primarily in children and the immunosuppressed.

Viral meningitis is typically caused by enteroviruses other than poliovirus. It is seen primarily in the summer months in infants and young children. Herpes simplex virus can cause a typically benign meningitis associated with primary genital tract infections. This is not to be confused with herpes simplex encephalitis, as discussed below.

Encephalitis is due primarily to viruses. Herpes simplex virus causes probably the most common form of viral encephalitis encountered in the developed world. It can occur in neonates and during reactivation of latent infection in adults. This form of herpes infection can produce necrotic lesions in the brain, resulting in long-term sequelae or death. Insect-borne viruses such as Eastern equine, Western equine, St. Louis, and La Crosse encephalitis viruses are encountered in the United States. In many states in the eastern United States, an epidemic of rabies in animals is occurring. It is only a matter of time before human cases are reported.

Fungal meningitis is seen primarily but not exclusively in the immunocompromised. It is of particular importance in AIDS patients, with *Cryptococcus neoformans* being far and away the most important cause of CNS infection in this patient population.

Parasites may also cause CNS infection. The most frequently encountered parasite causing CNS infections in the developed world is *Toxoplasma gondii*. These infections occur primarily in AIDS patients and represent reactivation of latent infections. In the developing world, one of the most common causes of a clinical presentation of meningitis/encephalitis is cerebral malaria. A major cause of adult onset of seizures in certain areas of the developing world where pork is a source of protein in the diet is cysticercosis. This disease occurs when eggs of the pork tapeworm *Taenia solium* are ingested. The parasite is unable to complete its life cycle, and cyst-like lesions occur throughout the body including the brain. An amoeba, *Naegleria fowleri*, causes a rare, fatal form of meningoencephalitis. It is found in

individuals living in temperate regions who swim in warm fresh water during the summer months.

Brain abscesses occur either through direct extension from a contiguous site, following trauma, or by hematogenous spread from another infected site. Typically, patients with abscesses due to hematogenous spread have either endocarditis or a lung abscess. Septic emboli, which are small blood clots containing infectious agents, are released from the primary infection site and enter the bloodstream. The embolus lodges in a capillary in the brain, causing a localized hemorrhage and producing a site for the initiation of infection which evolves into a brain abscess. The organisms most frequently causing abscesses in immunocompetent individuals are either *S. aureus* or organisms usually found in the oropharynx including the viridans group streptococci, *Actinomyces* spp., and anaerobic bacteria. In immunocompromised individuals, *Aspergillus*, *Mucor*, *Rhizopus*, and *Nocardia* spp. can cause brain abscess. In trauma patients, *S. aureus* and gram-negative rods are frequently seen. In diabetic patients, rhinocerebral mucormycosis can extend from the sinuses into the brain, causing extensive necrosis.

Your job will be to read through the Case Studies you have been provided with and, as a group, determine the etiologic agent for that disease as well as answer any of the questions associated with the Case Study you have been assigned.

Organism	General characteristics	Patient population	Disease manifestation
Bacteria			
Actinomyces spp.	Branching, gram-positive bacilli, usually anaerobic	Individuals with aspiration pneumonia	Brain abscess
Citrobacter diversus	Enteric gram-negative bacillus	Neonates	Meningoencephalitis with abscess
Clostridium botulinum	Toxin-producing, anaerobic, gram-positive bacillus	Infants, adults who ingest botulinum toxin	Botulism, flaccid paralysis
Clostridium tetani	Toxin-producing, anaerobic, gram-positive bacillus	Any, often associated with deep tissue wound	Tetanus, spastic paralysis
Coagulase-negative staphylococci	Catalase-positive, gram-positive cocci	Individuals with foreign bodies, e.g., shunts or bolts	Meningitis
Escherichia coli	Lactose-fermenting, gram-negative bacillus	Neonates	Meningitis
Group B streptococci *(Streptococcus agalactiae)*	Catalase-negative, gram-positive cocci	Neonates, immunocompromised adults	Meningitis
Haemophilus influenzae type b	Gram-negative, pleiomorphic bacillus	Unvaccinated children	Meningitis
Listeria monocytogenes	Catalase-positive, gram-positive coccobacillus	Neonates, immunocompromised adults	Meningitis
Mycobacterium tuberculosis	Acid-fast bacillus	Children; patients with AIDS	Tuberculous Meningitis
Neisseria meningitidis	Oxidase-positive, gram-negative diplococcus	All ages; outbreaks in college students & military	Meningitis
Nocardia spp.	Aerobic, partially acid-fast branching bacilli	Individuals with pulmonary nocardiosis	Brain abscess
Oral streptococci *(5. sanguis, S.*	Alpha-hemolytic, gram-positive cocci	Individuals with aspiration pneumonia	Brain abscess

Organism	General characteristics	Patient population	Disease manifestation
mutans, etc.)			
Prevotella sp., *Porphyromonas* sp.	Anaerobic, gram-negative bacilli	Individuals with aspiration pneumonia	Brain abscess
Pseudomonas aeruginosa	Oxidase-positive, gram-negative bacillus	Individuals with head trauma or foreign bodies	Meningitis
Staphylococcus aureus	Catalase-positive, gram-positive cocci	Individuals with head trauma or foreign bodies	Meningitis
Streptococcus pneumoniae	Catalase-negative, gram-positive cocci	Primarily young children and elderly	Meningitis
Fungi			
Aspergillus spp.	Acute-angle, septate hyphae in tissue	Immunocompromised with invasive aspergillosis	Brain abscess
Cryptococcus neoformans	Encapsulated, round yeast	Immunocompromised, especially AIDS	Meningitis
Mucor sp., *Rhizopus* sp.	Ribbon-like, aseptate hyphae in tissue	Diabetics, immunocompromised individuals	Necrotizing encephalitis, rhinocerebral mucormycosis
Parasites.			
Acanthamoeba sp	Amoeba	Immunocompromised or immunocompetent	Granulomatous amebic encephalitis or keratitis
Naegleria fowleri	Amoeba	Individuals with exposure to warm, fresh water	Fatal amebic meningoencephalitis
Plasmodium falciparum	Delicate, ring forms in blood	Individuals who visit malaria-endemic areas	Cerebral malaria
Taenia solium	larval cyst	Individuals who ingest *T. solium* eggs	Seizures, calcified lesions in brain or muscle
Toxoplasma gondii	large cysts in tissue	Immunocompromised, especially AIDS patients	Encephalitis, abscess
Viruses			
Echovirus/ coxsackievirus	Nonenveloped ssRNA	Children and adults during summer months	Aseptic meningitis
Encephalitis viruses	Both enveloped and non enveloped ssRNA	Children and adults bitten by viral arthropod vector	Encephalitis, frequently fatal
Herpes simplex virus	Enveloped *dsDNA*	Neonates, individuals with primary genital herpes, individuals with primary or recurrent herpes infections	Necrotizing encephalitis; benign, aseptic meningitis; necrotizing hemorrhagic encephalitis
Human immunodeficiency virus (HIV)	Enveloped retrovirus	AIDS	AIDS-associated dementia; predisposes to other CNS' infections
Poliovirus	Nonenveloped ssRNA	Nonvaccinated individuals; live, attenuated vaccine, especially in the immunocompromised	Polio paralysis
Rabies virus	Enveloped ssRNA	Individuals bitten or scratched by nonvaccinated, rabid dog, cat, or other mammal	Rabies

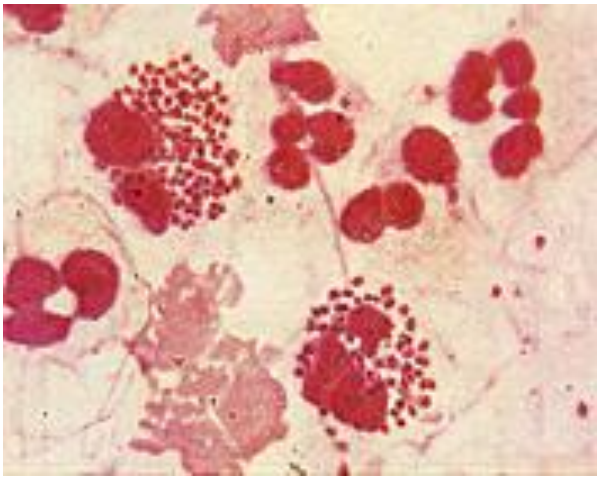
Case One

A white male, 17 years of age presented at the emergency room with a severe headache, vomiting, and a stiff neck with pain running up his back. On admission, his temperature was 101F. The young man appeared to have trouble hearing during the nurse's interview and also seemed to have trouble concentrating.

The history revealed that the young man is a wrestler for the local high school team. He had felt as though he were getting a cold the past few days, since his last meet in Hicksville. He did not smoke or drink, but he had attended a party two days earlier thrown by his girlfriend and the other cheerleaders to celebrate his victory in the sectionals. He had been holding his weight at 162 for the season, so he ate little and did not drink on the day of meets (today is a day of the meet).

On physical exam, the physician noticed several areas of small purplish spots on the skin of the back, thigh and arm. The boy thought those were from wrestling.

1. What is the disease and what is the most likely etiological agent?
2. Which were the critical factors in your choice of diagnosis?
3. What will most likely happen if the disease is not treated?
4. What would you prescribe to treat this disease and why?



Case Two

Sixty-year-old Mr. R. was brought to the hospital with confusion, right-sided weakness, and fever. His daughter, who was visiting him, reported that when she arrived he thought "there were devils in the room." On the way to the hospital he hallucinated intermittently, telling her that he smelled roses. Three days previously he had complained of mild nausea and vomited once. When he arrived at the emergency department, Mr. R. had a generalized seizure.

A CT scan of the head was normal, but a magnetic resonance imaging (MRI) scan documented T1-hypointense and T2-hyperintense signal in the cortex and gray–white matter junction in the left temporal lobe. CSF obtained by lumbar puncture contained 50 WBCs/mm^3 (90% mononuclear cells) and 300 RBCs/mm^3, glucose in the normal range (70 mg/dL), and elevated protein (100 mg/dL). CSF was sent for bacterial and viral culture. An electroencephalogram (EEG) revealed periodic high-voltage spike wave activity from the left temporal region.

Intravenous acyclovir was started immediately. Mr. R. was continued on intravenous acyclovir for 3 weeks, which halted the progression of his neurological symptoms. However, he had many residual signs of neurological impairment and required extensive rehabilitation therapy.

1. What microbe is most likely causing this patient's symptoms?
2. What is the best single diagnostic method to establish this diagnosis
3. What is the prognosis for patients who survive this disease?

Case Three

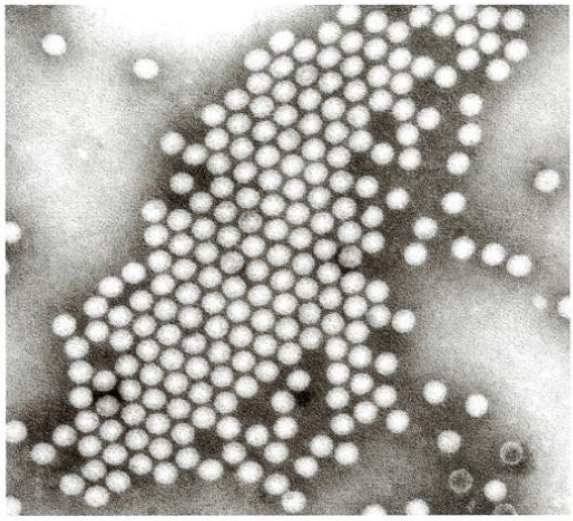
The patient was a 36-year-old female who worked in a fast-food restaurant. At 4 p.m. on the day prior to admission, the patient told a coworker that she felt "dizzy" and thought she had been "drugged." She awoke at 3:00 a.m. on the day of admission and reported that her tongue was "thick" and she was having difficulty swallowing. On physical examination, she was weak and somnolent but her tongue and epiglottis appeared normal. She did not have a fever, rash, or any ticks on her skin. She gave no history of recent flu-like illness, tick bites, exposure to toxic chemicals, or ingestion of shellfish. Her condition worsened and she developed descending quadraparesis, requiring intubation. Cultures of stool, gastric contents, and food samples from her home were negative. A serum test revealed the etiology of her illness and an electromyogram (EMG) supported the diagnosis. She received approximately 6 weeks of supportive care, including 5 weeks of ventilatory assistance, and eventually returned to her baseline state of health.

1. What was wrong with this patient? Did she have an infection? Explain.
2. What serum test was done to diagnose her disease? Explain how it is done.
3. Explain the purpose behind culturing the different patient and environmental specimens.
4. Describe the three different forms of this disease and the epidemiology of each. Which form did this patient have?
5. Explain the pathogenesis of her disease.
6. What is appropriate therapy in this patient?

Case Four

Cape Verde, 2000: Between 16 August and 17 October 2000, 33 cases of acute flaccid paralysis, including 7 (21%) deaths, were reported in Cape Verde, an archipelago of 10 islands west of Senegal and Mauritania. The first patient was a child aged 2 years from the capital city of Praia; the onset of paralysis occurred on 16 August. Twenty-two cases were reported from the island of Sao Tiago, seven from Sal, three from Sao Vicente, and one from Maio. The ages of the acute flaccid paralysis patients ranged from 3 months to 38 years. The estimated population of Cape Verde in 2000 was 437,500 (World Health Organization, unpublished data, 2000). The reported routine vaccination coverage had been <80% every year since 1995.

In addition to paralysis, those who were affected had experienced stiffness in the neck, flu-like symptoms, and diarrhea. The viral pathogen, identified by enzyme-linked immunosorbent assay, was a positive-sense, single-stranded ribonucleic acid (RNA) virus with a polyhedral capsid belonging to the picornavirus family (TEM is shown below).



1. What disease was involved in this outbreak?
2. Identify the pathogen and describe how it is typically transmitted.
3. How does the virus cause paralysis?
4. Would you have expected more than 33 people to have been infected by this virus during the outbreak?
5. In order to minimize the number of deaths and cases of the disease, how would you have managed the outbreak?