Lecture 30: Microbial Diseases of the Nervous System

Unlike the skin, the central nervous system and peripheral nervous system have no native flora.
- Surrounding the brain and spinal cord are a set of continuous membranes, the meninges; cerebrospinal fluid circulates between the two innermost meninges (Tortora et al., Figure 22.2).
- An interesting feature of the central nervous system, with relevance to infection, is the blood-brain barrier:
  - Tissues of the central nervous system are served by specialized capillaries that are more selective than most capillaries in allowing passage of molecules.
  - As a result, many antimicrobial drugs are unable to reach the tissues of the central nervous system, complicating treatment.
  - On the other hand, the blood-brain barrier may serve as a nonspecific defense against infection.
- Microorganisms may infect the central nervous system:
  - Trauma can interrupt the normal barriers, and some microorganisms move along peripheral nerves.
  - The most common route for infection of the central nervous system is probably through lymphatic vessels.
- Infection of the meninges is called meningitis, while infection of the brain itself is called encephalitis.

Bacterial meningitis can be caused by a variety of bacteria, especially trauma allows introduction of normal flora or environmental material to the central nervous system; however, greater than 80% of cases are caused by three species (Tortora et al. Table 22.1):
- Neisseria meningitidis, the agent of meningococcal meningitis, is found as part of the respiratory tract flora of some persons.
  - Throat infection of a susceptible host can lead to bacteremia, then to invasion of the cerebrospinal fluid.
  - N. meningitidis resists killing by phagocytes, which may aid its invasion of the central nervous system.
  - Pathogenesis of meningococcal meningitis is related to the effects of N. meningitidis endotoxin.
  - In the past, outbreaks of meningococcal meningitis were common in military training facilities.
  - Concern with outbreaks at colleges has led to more widespread use of a vaccine for meningococcal meningitis.
- Haemophilus influenzae was once an important agent of bacterial meningitis in young children.
  - The genus name of H. influenzae comes from its requirement for growth factors in blood; the species name comes from an erroneous assignment of H. influenzae as the agent of influenza (which is a viral infection).
  - The type b strain of H. influenzae is responsible for most cases of H. influenzae meningitis.
  - A vaccine, prepared from capsular antigens of H. influenzae type b, is currently recommended for children at the age of two months.
- Streptococcus pneumoniae, the most important agent of bacterial pneumonia, is also a significant cause of bacterial meningitis.
  - Although most cases of pneumococcal meningitis occur in infants, compromised elderly patients are also susceptible.
  - Mortality due to pneumococcal meningitis is relatively high for a bacterial infection.

Listeria monocytogenes, associated with a variety of animals, can cause meningitis in humans:
- When acquired, the usual course of L. monocytogenes infection is a mild gastrointestinal infection - listeriosis.
- *L. monocytogenes* does have affinity for the central nervous system, especially in immunosuppressed hosts and in pregnant women
  - When it infects a pregnant woman, growth of *L. monocytogenes* on the placenta leads to a high rate of miscarriage and stillbirth
  - *L. monocytogenes* is the leading cause of meningitis in immunosuppressed cancer patients
- *L. monocytogenes* is usually acquired from contaminated food products, and will grow at refrigerator temperatures

*Tetanus* and *botulism* are diseases resulting from the action of exotoxins produced by bacteria belonging to the genus *Clostridium*
- *Clostridium tetani* is especially common in soils contaminated with animal feces
  - *C. tetani* is capable of growth in deep puncture wounds, where anaerobic conditions can develop
  - The exotoxin produced by *C. tetani*, *tetanospasmin*, is an extremely potent neurotoxin that blocks the signals that normally signal muscle relaxation, leading to spastic paralysis
  - Tetanus can usually be prevented by administration of toxoid immediately after potential exposure; the bacteria grow slowly enough to allow an adequate immune response to tetanospasmin
  - *Tetanus immune globulin (TIG)* can also be administered; this is an example of artificially acquired passive immunity
- *Clostridium botulinum*, the agent of botulism, is actually unable to grow in tissues of adult humans
  - Most cases of botulism arise from ingestion of *botulin toxin* produced by *C. botulinum* that has grown in inadequately sterilized foods
  - Several types of botulin toxin are produced by different strains of *C. botulinum*
  - *Infant botulism* is caused by growth of *C. botulinum* in the gastrointestinal tract of infants, whose normal gastrointestinal flora is different from that of adults; 30% of cases of infant botulism have been associated with ingestion of *C. botulinum* endospores in honey

*Mycobacterium leprae*, the bacterial agent of leprosy or *Hansen’s disease*, multiplies in the peripheral nervous system
- *M. leprae* grows very slowly and has never been grown on artificial media; research on its biology is conducted in armadillos
- The lesions characteristic of leprosy, like those of tuberculosis (caused by another *Mycobacterium* species, *M. tuberculosis*), are associated with cell-mediated immune responses to intracellular growth of the pathogen
- Despite its reputation, leprosy is not especially contagious
- Although difficult to treat, leprosy does respond to long-term antibiotic therapy
- There is some hope that leprosy, a disease only of humans, might be eradicated

The viral infection *poliomyelitis* is best known from its most severe manifestation, paralysis
- Actually, before polio vaccines were available, infection with *poliovirus* was rather common
- Poliovirus is acquired via the fecal-oral route
  - The majority of infections are limited to the gastrointestinal tract
  - Even when the infection becomes systemic, it only enters the central nervous system in 1-2% of infections
- Pathogenesis of the paralytic form of polio results from destruction of motor nerve cells in the upper spinal cord
- The availability of vaccines has markedly reduced the incidence of poliomyelitis in the United States (Tortora et al., Figure 22.10), and worldwide eradication is underway

*Rabies*, though rare in humans, is greatly feared since once an infection is established, it is invariably fatal.
- **Rabies virus** has a characteristic "bullet" shape and is acquired through broken skin from the saliva of an infected animal
- The virus can cross intact mucous membranes, and has been transmitted by mechanisms other than animal bites
- Fortunately, rabies virus exhibits a long incubation period, and an adequate level of artificially acquired active immunity can be produced before the virus invades the nervous system
  - The original treatment, developed by Pasteur (perhaps his greatest claim to fame), used dessicated spinal cords from rabbits infected with rabies virus
  - Today, treatment involves use of viral material that has been grown on human cells in culture, then inactivated

**Arthropod-borne encephalitis** describes a number of diseases caused by related viruses: the **arboviruses**
- All of these viruses are transmitted between mammalian hosts by mosquitoes
- The animal hosts for the arboviruses vary; for some, the main reservoir is birds
- Arthropod-borne encephalitis infections are seasonal, following the abundance of the mosquito vectors
- The most serious (and one of the rarest) form of arthropod-borne encephalitis in the United is **Eastern equine encephalitis (EEE)**; the "equine" means that horses are also susceptible, not that they are the main reservoir
- **West Nile encephalitis**, which recently entered the United States, is another arboviral infection

Additional diseases of the central nervous system
- **Cryptococcosis**, caused by the fungus *Cryptococcus neoformans*, may result in chronic meningitis in immunocompromised persons
- **Trypanosomiasis**, "African sleeping sickness", is a serious vector-borne infection in central and eastern Africa
  - The agent of trypanosomiasis, *Trypanosoma brucei*, is a flagellate protozoan
  - Immune control of trypanosomiasis is complicated by the phenomenon of "antigenic variation" (Tortora et al. Figure 22.15)
- **Naegleria meningoencephalitis**, caused by the protozoan *Naegleria fowleri*, is a rapidly fatal brain infection acquired from water
- The importance of *prions* in neurological disease is becoming more appreciated
  - Most human prion diseases are inherited or of unknown etiology; the most common (neverthless rare) of these is **Creutzfeldt-Jakob disease (CJD)**
  - There is current concern that new variant CJD (nvCJD) might be acquired by ingestion of beef carrying *bovine spongiform encephalopathy (BSE)*