8. PATHOGENESIS AND CLASSIFICATION OF CENTRAL NERVOUS SYSTEM INFECTION

by Marko Pokorn
Department of Infectious Diseases, University Medical Centre, Zaloška 7, SI-1000 Ljubljana, Slovenia

8.1 Abstract

The infections of the central nervous system (CNS) differ from infections of other organ systems. Numerous infections of the CNS can progress rapidly and cause substantial damage or even death if they are not recognized and treated promptly and aggressively. Viruses, bacteria, fungi, protozoa and helminths infect the CNS, the clinical picture depends on the infecting agent, the site of infection and the host factors. The most common form of CNS infection is acute meningitis of viral etiology, a benign, self-limited disease, whereas the most severe form is bacterial meningitis. The infections of the CNS represent a continuous spectrum of overlapping clinical syndromes from benign self-limiting diseases to severe and life-threatening infections. Prompt and accurate diagnosis is necessary for proper treatment. Therefore, close cooperation between clinicians and the laboratory is mandatory.

8.2 Introduction

Infectious diseases of the central nervous system (CNS) differ from infections of other organ systems in many ways. CNS is different from other organ systems, it is contained within a rigid skull, surrounded by layers of meninges and it contains no lymphatics.

Numerous infections of the CNS can progress rapidly and cause substantial damage or even death if they are not recognized and treated promptly and aggressively. Physicians have, therefore, to be aware of the possibility of CNS infections in their patients. The common clinical manifestations suggesting infection of the CNS include altered consciousness, headache and other signs of increased intracranial pressure (vomiting, cardiovascular and respiratory signs), seizures and focal signs of CNS dysfunction. Apart from these, signs of infection (predominantly fever) are often present.

8.3 Pathogenesis of CNS infection

The pathogenic organisms gain access to the CNS predominantly by haematogenic spread. Viruses usually first colonize the mucosal surfaces throughout the body, then they enter the blood. Prior to invading the CNS, they usually multiply at extraneural sites and then cross the blood-brain barrier. Most viruses enter the CNS directly through the cerebral capillary endothelial cells, some enter via the choroid plexus and some viruses are carried through the barrier by the infected leukocytes. Certain viruses can reach the CNS via the olfactory nerve and peripheral nerves. The mode of entry into the CNS also influences the mode of spread of the virus within the CNS.

In bacterial infections of the CNS, the first event is usually mucosal colonization in the nasopharynx. Most bacterial pathogens possess surface characteristics that enhance mucosal colonization. After gaining access to the bloodstream bacteria have to survive host defence mechanisms. They achieve that by means of a polysaccharide capsule that resists phagocytosis by neutrophils and classic complement-mediated bactericidal activity. The exact mechanism of meningeal invasion by bacteria is not known, probably a sustained bacteraemia plays a role. After bacteria gain access to the subarachnoid space, local host defences are inadequate to control the infection. The induction of an intense inflammatory response in the subarachnoid space by meningeal pathogens contributes to many of the pathophysiologic consequences of bacterial meningitis and therefore to significant morbidity and mortality from this disorder. It is caused by the release of inflammatory mediators in the CNS. In the course of bacterial meningitis, the permeability of the blood-brain barrier increases. An important event in the course of bacterial meningitis is cerebral oedema, caused by vasogenic, cytotoxic or interstitial mechanisms. It contributes to increased intracranial pressure and may result in life-threatening cerebral herniation. Cerebral blood flow is decreased during bacterial meningitis, and relative anoxia follows, further contributing to neuronal damage.

In cases of localized purulent infections within the CNS, bacteria originate from adjacent foci of infection, such as otitis, sinusitis, mastoiditis or septic phlebitis, or alternatively bacteria may arrive via septic emboli from distant sites of infection (e.g. infected heart valve).

In certain viral and mycoplasmal infections as well as following immunizations, immune response is elicited not only against the infecting agent but also against myelin basic protein. The immune response against myelin in the peripheral nerves and nerve roots causes peripheral nerve dysfunction, when the CNS myelin is affected, acute disseminated encephalomyelitis ensues.

8.4 Clinical syndromes of CNS infection

8.4.1 Acute meningitis

Meningitis represents inflammation of meninges and is recognized by an increased number of leukocytes in the cerebrospinal fluid (CSF). On the basis of gross appearance and leukocyte content of the CSF, aseptic and purulent meningitis can be distinguished. Aseptic meningitis is more common and it is usually caused by viruses. Enteroviruses are the most common cause of viral meningitis. The disease can occur in epidemics, it is most common in late summer and early fall. In Slovenia, tick-borne encephalitis virus is the second most common cause of viral meningitis. While
viral meningitis is a mild disease with a self-limiting course, bacterial or purulent meningitis is a medical emergency. Depending on the causative agent and host factors, it carries substantial morbidity and mortality. It is usually caused by Streptococcus pneumoniae and Neisseria meningitidis.

Since the introduction of vaccination Haemophillus influenzae type b meningitis has been observed very rarely. The clinical features of meningitis and the spectrum of potential pathogens depend on the host risk factors. In Table 1, the causative agents of bacterial meningitis in various age and risk groups are shown. In a patient with suspected meningitis, lumbar puncture and examination of the cerebrospinal fluid (CSF) has to be performed immediately. The typical CSF findings in bacterial (purulent) meningitis are shown in Table 2.

Table 1. Common bacterial pathogens based on predisposing factors in patients with meningitis (from Mandell GL, Bennett JE, Dolin RE. Principles and practice of infectious diseases, 5th ed.)

| Predisposing factor - Age | Common bacterial pathogens |
|--------------------------|----------------------------|
| 0-4 weeks                | S. agalactiae, E. coli, L monocytogenes, K. pneumoniae, Enterococcus spp., Salmonella spp. |
| 4-12 weeks               | S. agalactiae, E. coli, L monocytogenes, H. influenzae, S. pneumoniae, N. meningitides |
| 3 months – 18 years      | H. influenzae, N. meningitides, S. pneumoniae |
| 18-50 years              | S. pneumoniae, N. meningitides |
| >50 years                | S. pneumoniae, N. meningitides, L. monocytogenes, aerobic Gram-negative bacilli |
| Immunocompromised state  | S. pneumoniae, N. meningitides, L. monocytogenes, aerobic Gram-negative bacilli (including P. aeruginosa) |
| Basilar skull fracture   | S. pneumoniae, H. influenzae, group A/E haemolytic streptococci |
| Head trauma; postneurosurgery | S. aureus, S. epidermidis, aerobic Gram-negative bacilli (including P. aeruginosa) |
| CSF shunt                | S. epidermidis, S. aureus, aerobic Gram-negative bacilli (including P. aeruginosa), Propionibacterium acnes |

Table 2. Characteristical CSF findings in bacterial meningitis.

| Parameter                | Value |
|--------------------------|-------|
| CSF pressure             | > 180 mm Hg |
| Protein content          | > 1.5 g/L |
| Glucose                  | < 2.22 mmol/L |
| White blood cells        | > 1000-5000/mL (from < 100 to > 10000/mL) |
| Percent of neutrophils   | > 80% |
| Gram stain               | Positive in 60-90% |
| Antigen                  | Positive in 50-100% |
| CSF culture              | Positive in 70-85% |

The clinicians have a difficult task to distinguish between viral and initial bacterial meningitis. CSF findings that are individual predictors of bacterial meningitis with 99% certainty are CSF glucose <1.9 mmol/L, a CSF-to-blood glucose ratio of 0.23, CSF protein concentration above 2.2 g/L, CSF white blood cells above 2000/mL or CSF neutrophils above 1160/mL. The presence of atypical lymphocytes in the CSF is highly suggestive of viral meningitis, but lymphocyte prevalence does not exclude pyogenic bacterial infection. Gram stain of the CSF is a very useful test and its yield is related to the bacterial content of the CSF. Gram stain is positive in 25% of cases with bacterial content of 103 colony-forming units (CFU)/mL, in 60% of CSF samples with 103-104 CFU/mL and in 97% of CSF samples with >105 CFU/mL. With Gram staining, bacteria can be seen in 60-90% of purulent meningitis cases with a nearly 100% specificity. In patients pretreated with antibiotics, Gram stain is positive in 40-60% of cases and CSF culture is positive in <100%.

Not all bacteria evoke such a dramatic clinical picture. Treponema pallidum, the causative agent of syphilis and Borreia Burgdorferi, which causes Lyme disease, can cause aseptic meningitis, characteristically with a lymphocyte predominance in the CSF. These infections have a protracted clinical course with fluctuating signs and symptoms, and the classical signs of CNS infection are often absent.

8.4.2 Chronic meningitis

Chronic meningitis is defined as the persistence of clinical signs and symptoms and CSF pleocytosis for more than 4 weeks. The syndrome has many infectious and non-infectious causes, most of them carrying high morbidity and mortality. Establishing the cause of chronic meningitis is essential for successful treatment. In Table 3, infections of the CNS causing chronic meningitis and the usual mode of presentation are presented.

Table 3. Infectious diseases that may manifest as chronic meningitis: usual presentation in the CNS (from Mandell GL, Bennett JE, Dolin RE. Principles and practice of infectious diseases, 5th ed.)
The CSF findings are not pathognomonic. Lumbar puncture has to be performed repeatedly, both for following the meningeal inflammation and obtaining cultures. Various microbiological methods have to be used, but for many diseases, CSF cultures remain the diagnostic standard. In searching for the cause of chronic meningitis one always has to bear in mind that some diseases having a different etiology and requiring different treatment mimic chronic meningitis.

### 8.4.3 Encephalitis & myelitis

The term encephalitis denotes inflammation of brain and myelitis denotes the inflammation of spinal cord. Because meningeal inflammation frequently accompanies these syndromes, the terms meningoencephalitis and meningoencephalomyelitis are often used. When infectious agents reach the CNS, only certain cells may be infected. The involvement of specific cell types and various regions of the brain gives rise to specific clinical signs. The causes of encephalomyelitis are shown in Table 4.

| Meningitis                            | Focal lesion                            | Encephalitis                        |
|--------------------------------------|-----------------------------------------|-------------------------------------|
| Acanthamoeba infection               | Actinomycosis                           | African trypanosomiasis             |
| Angiostrongylus cantonensis infection | Blastomycosis                           | Cytomegalovirus infection           |
| Brucellosis                          | Cerebritis                               | Enterovirus in pts with hypogammaglobulinemia |
| Candidiasis                          | Cysticercosis                           | Muscles(SEP)                        |
| Coxiella              | Molds (strep, staphylococcus, pseudallescheriasis) | Rabies                             |
| Cryptococcosis                      | Nocardiosis                             | Viral encephalitis                  |
| Histoplasmosis                      | Schistosomiasis                         |                                    |
| Lyme disease                        | Toxoplasmosis                           |                                    |
| Sporotrichosis                      |                                        |                                    |
| Syphilis                             |                                        |                                    |
| Tuberculosis                         |                                        |                                    |

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#### Table 4. Viral, post-viral and non-viral causes of encephalomyelitis (from Mandell GL, Bennett JE, Dolin RE. Principles and practice of infectious diseases, 5th ed.)

| Viral infection | Post-viral infection | Non-viral |
|----------------|----------------------|----------|
| Herpes simplex types 1 and 2 | Rubella | Typhus |
| varicella-zoster virus | Influenza | Amebiasis |
| herpes B virus, Epstein-Barr virus | Mumps | Q fever |
| cytomegalovirus, human herpesvirus | Measles | Chlamydia |
| variola virus | Vaccinia | Mycobacteria |

In the CSF, a pleocytosis usually is present. Early in the course of encephalitis, the CSF can be normal. A repeat lumbar puncture has to be performed in 24 hours to ascertain the presence of pleocytosis. Increased numbers of erythrocytes can be present in the CSF of patients with herpes encephalitis, Naegleria infection and acute necrotizing hemorrhagic leukoencephalitis. The protein content of the CSF is usually increased and in the convalescent phase, specific antibodies are synthesized within the CSF. Gram stain for bacteria should be performed as well as acid-fast stain for mycobacteria and India ink for cryptococci. PCR has become the gold standard for the detection of herpes simplex virus. It can also be used for the detection of other herpesviruses.

Therapy for viral causes of encephalitis is limited to acyclovir for herpes simplex, varicella-zoster and herpes B virus encephalitis, ganciclovir and foscamet for cytomegalovirus encephalitis and antiretroviral therapy for HIV-associated neurologic disease. For most nonviral causes of encephalitis, specific therapy is available.

#### 8.4.4 Brain abscess, subdural & epidural empyema

Brain abscess is one of the most serious complications of head and neck infections. It can be caused by bacteria, fungi, protozoa and helminths. The microorganisms reach the brain from an adjacent focus of infection, such as the middle ear, mastoid process or paranasal sinuses, they can spread from distant foci via the bloodstream or can be introduced by trauma (open cranial fracture, neurosurgical procedure, foreign-body injury). The causative agents are related to the primary site of infection and to the specific host factors, predominantly immune status. CT scanning has greatly improved the diagnosis of brain abscess and MRI provides better information about the lesions.
A patient with a brain abscess should be managed by a team consisting of a neuroradiologist, neurosurgeon and infectious disease specialist. A neurosurgical intervention is required for both therapeutic and diagnostic purposes. The extent and size of the lesion(s) determine the surgical intervention. The initial antibiotic therapy is empirical and should be further adjusted according to the susceptibility of clinical isolate(s).

The subdural space between the dura and the subarachnoid membrane is traversed by veins and is divided into several large compartments. Subdural empyema is usually caused by aerobic and anaerobic bacteria which reach subdural space via the emissary veins and from the skull. The origin is predominantly the sinuses, followed by the middle ear and the mastoid. Metastatic infection is rare. Subdural empyema can result from neurosurgical procedures, trauma and can represent a complication of purulent meningitis. It is manifested by meningeal signs and a focal neurologic deficit. CT or MRI demonstrates empyema. Treatment usually includes antibiotics and surgical intervention.

Epidural abscess is localized between the bony skull and the outer layer of the dura. It is frequently accompanied by local osteomyelitis. The mode of development and bacteriology of epidural abscess is similar to that of subdural abscess. Treatment involves surgical drainage and antibiotic therapy.

In conclusion, the infections of the CNS represent a continuous spectrum of overlapping clinical syndromes from benign self-limiting diseases to severe and life-threatening infections. Prompt and accurate diagnosis is necessary for proper treatment. Therefore, close cooperation between clinicians and the laboratory is mandatory.

References

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Page 71