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Infections of the Nervous System

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ABSTRACT

Microorganisms can affect the entire neuraxis, producing a variety of neurologic complications that frequently entail prolonged hospitalizations and complicated treatment regimens. The spread of pathogens to new regions and the reemergence of opportunistic organisms in immunocompromised patients pose increasing challenges to health care professionals. Because rapid diagnosis and treatment may prevent long-term neurologic sequelae, providers should approach these diseases with a structured, neuroanatomic framework, incorporating a thorough history, examination, laboratory analysis, and neuroimaging in their clinical reasoning and decision-making.

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INTRODUCTION

The approach to neurologic infections, like systemic infections, necessitates a detailed knowledge of the patient's medical history, demographics, and immune status. Pathogens have the propensity to attack all areas of the nervous system, causing distinct clinical syndromes. Consequently, a focused neurologic history and examination are fundamental to early and accurate diagnosis. We provide a basic neuroanatomical framework, highlighting prevalent infections in the community and neurologic diseases in the immunocompromised patient.

INFECTIONS OF THE CENTRAL NERVOUS SYSTEM

Meningitis

Meningitis, most typically an inflammation of the leptomeninges and subarachnoid space, is a neurologic emergency. Because the clinical triad of fever, neck stiffness, and altered mental status accounts for only 44% of adult patients with bacterial meningitis, providers should have a high level of suspicion.[1] Headaches and photophobia are common features. Impaired sensorium, hemodynamic instability, and respiratory compromise are life-threatening complications that require intensive care unit monitoring.[2] Gram stain and culture from blood and cerebrospinal fluid are critical for diagnosis. Immunocompromised patients or adults with focal neurologic signs, seizures, obtundation, or papilledema should undergo a noncontrast head computed tomography scan prior to lumbar puncture.[3] Guidelines recommend initiating antibiotics as soon as possible, even prior to lumbar puncture if this study is delayed.[3]

Bacterial agents cause a fulminant syndrome with high-grade fevers, sepsis, or end organ damage. Among adults from developed countries, the most common organisms are *Streptococcus pneumoniae*, followed by *Neisseria meningitidis*.[4] Immunocompromised hosts and individuals over 50 are more susceptible to *Listeria monocytogenes.* The cerebrospinal fluid opening pressure is frequently elevated. At least one of the following cerebrospinal fluid markers—white blood cell count >2000 cells/mm^3, protein >2.2 g/L, glucose level <34 mg/dL, and cerebrospinal fluid-to-serum glucose ratio of <0.23—are present in 88% of bacterial meningitis cases.[1,2] Gram stain has a sensitivity of 60% to 90% and a specificity of over 97%.[1] Empiric treatment includes vancomycin and a third-generation cephalosporin to cover the most common agents, including those resistant to beta-lactam antibiotics.

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Ampicillin may be added for *Listeria* coverage.[3] Intravenous steroids administered with the first dose of antibiotics likely confer a decreased mortality in *S. pneumoniae* infection and are recommended in the bacterial meningitis treatment guidelines.[3,5]

Viruses, the most common cause of meningitis, typically produce a self-limiting and less severe infection.[6] Because clinical features insufficiently distinguish microorganisms, a lumbar puncture is still necessary. In Western countries, the most common agents are Enteroviruses, followed by herpes simplex virus-2 (HSV-2), varicella zoster virus (VZV), and arboviruses in order of prevalence.[6,7] The cerebrospinal fluid profile usually reveals a mild to moderate lymphocytic pleocytosis (100-1000 cells/mm^3), moderately elevated protein, and normal glucose.[7] Although molecular testing with polymerase chain reaction has enabled the identification of common viruses, in many cases, the pathogenic agent remains unknown. The treatment is largely supportive, and despite the evidence for acyclovir in HSV encephalitis, its efficacy in HSV meningitis is unclear.[6]

CLINICAL SIGNIFICANCE

- Pathogens can attack all areas of the nervous system, causing distinct deficits.
- Cerebral spinal fluid analysis and neuroimaging are key diagnostic studies.
- Meningoencephalitis is a neurologic emergency that requires immediate recognition.
- Atypical infections will increase as more patients take immunosuppressant drugs.

Providers must consider *Mycobacterium tuberculosis* in immunocompromised patients or individuals from developing countries. Tuberculous meningitis typically presents as an indolent illness with headaches, fevers, and photophobia over days to weeks.[8] The bacterium infiltrates the skull base and can cause cranial neuropathies, subcortical strokes, or obstructive hydrocephalus.[8,9] Cerebrospinal fluid analysis varies, but usually reveals protein >100 mg/dL, white blood cell count 50-1000 cells/mm^3, mixed neutrophilic and lymphocytic cells, and glucose <50% serum concentration.[4,10] Acid-fast bacilli staining and culture have poor sensitivity, which causes diagnostic and therapeutic delays.[10] Consequently, the World Health Organization now recommends gene amplification assays for rapid detection within the cerebrospinal fluid.[11] Treatment entails antituberculosis chemotherapy for 9-12 months and adjunctive corticosteroids.[12]

Yeasts, molds, and dimorphic fungi are also culprits for meningitis and, similar to *M. tuberculosis*, can present more indolently with basilar features and a mixed cerebrospinal fluid pleocytosis of varying severity.[13] Additional cerebrospinal fluid features are typically hypoglycorrhachia and elevated protein. Cerebrospinal fluid fungal cultures have a notoriously low sensitivity but high specificity.[14] *Cryptococcus* species are the most common cause of fungal meningitis, especially in the immunocompromised. The diagnosis relies on a positive cerebrospinal fluid cryptococcal antigen.[15] An elevated opening pressure has important implications, because guidelines recommend serial lumbar punctures or a neurosurgical drain to reduce the intracranial pressure.[16] Fungal meningitis treatment varies by organism; for *Cryptococcus*, induction with amphotericin B and 5-flucytosine, followed by consolidation with fluconazole, is standard.[17]

Encephalitis

Encephalitis is an inflammation of the brain parenchyma that arises from penetration of the blood–brain barrier or overlying meningitis.[18] Some pathogens have a proclivity for specific neuroanatomical structures, producing distinct deficits. HSV represents only 10%-15% of viral encephalitis cases, but carries a high morbidity and mortality if untreated early.[18] HSV-1, a more common cause of encephalitis than HSV-2, remains latent in trigeminal ganglia.[19] In primary infection or reactivation, the virus spreads via sensory fibers to the meninges neighboring the orbitofrontal and mesial temporal lobes.[20] Individuals present with headaches, fevers, and a limbic encephalitis, characterized by behavioral changes and seizures.[18,20] Examination may reveal amnesia, aphasia, visual field impairment, or altered sensorium.[18] The brain magnetic resonance imaging (MRI) study shows increased T2 signal, hemorrhage, or contrast enhancement in the temporal lobes (**Figure 1**).[19,20] A positive HSV polymerase chain reaction from the cerebrospinal fluid is diagnostic. Although intravenous acyclovir significantly reduces the mortality, neurologic sequelae may persist months to years after treatment.[20]

Mosquito and tickborne viruses mediate encephalitis between spring and autumn.[21] West Nile virus, the most common domestic arbovirus, is endemic to the entire continental United States and is responsible for over 1700 deaths to date.[21] Fewer than 1% of infected individuals develop neuroinvasive disease, and adults over age 65 years are at highest risk.[22,23] West Nile fever, characterized by fevers, malaise, myalgias, and skin rash precedes meningoencephalitis.[24] An acute flaccid paralysis, a unique manifestation of West Nile virus, arises from anterior horn cell destruction.[25] Neuroimaging shows abnormal signal in the basal ganglia, thalami, upper brainstem, or anterior spinal cord.[24] Detection of West Nile virus immunoglobulin (Ig)M from the cerebrospinal fluid is diagnostic. Because no specific antiviral agents are available, the treatment is supportive.

Other neurotropic arboviruses have emerged as prominent causes of encephalitis in North America. Powassan virus, a tick-borne *flavivirus,* causes a systemic illness with confusion or focal neurologic deficits primarily in the Great Lakes and Northeast.[26,27] MRI findings reveal subcortical gray matter, brainstem, or cerebellar involvement.[26] Pathogen identification requires Powassan antibodies in the serum or cerebrospinal fluid. Because Powassan serologies may be absent from state arbovirus lab panels, clinicians should request dedicated testing when suspicion is high.