

Pearls: Infectious Diseases

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ABSTRACT

Neurologists have a great deal of knowledge of the classic signs of central nervous system infectious diseases. After years of taking care of patients with infectious diseases, several symptoms, signs, and cerebrospinal fluid abnormalities have been identified that are helpful time and time again in determining the etiological agent. These lessons, learned at the bedside, are reviewed in this article.

KEYWORDS: Herpes simplex virus, Lyme disease, meningitis, viral encephalitis

CLINICAL MANIFESTATIONS

- Although the “classic triad” of bacterial meningitis is fever, headache, and nuchal rigidity, vomiting is a common early symptom. Suspect bacterial meningitis in the patient with fever, headache, lethargy, and vomiting (without diarrhea). Patients may also complain of photophobia. An altered level of consciousness that begins with lethargy and progresses to stupor during the emergency evaluation of the patient is characteristic of bacterial meningitis.
- Fever (temperature $\geq 38^{\circ}\text{C}$ [100.4°F]) is present in 84% of adults with bacterial meningitis and in 80 to 94% of children with bacterial meningitis.^{1–3} Symptoms of bacterial meningitis are often preceded by an upper respiratory tract infection, sinusitis, or otitis media.
- The rash of meningococemia begins with petechial lesions on the trunk and lower extremities, in the mucous membranes and conjunctiva, and occasionally on the palms and soles. The meningococcal vaccine does not contain serogroup B, which is responsible for one third of cases of meningococcal disease. Thus, a history of having been vaccinated does not rule out meningococcal disease.
- Viral meningitis is a syndrome of fever, headache, nausea, photophobia, and meningismus. The patient

does not have an altered level of consciousness, seizures, or focal neurologic deficits.

- The rash of a viral exanthema typically involves the face and chest first then spreads to the arms and legs. This can be an important clue in the patient with headache, fever, and stiff neck that the meningitis is due to echovirus or coxsackievirus.
- Suspect tuberculous meningitis in the patient with either several weeks of headache, fever, and night sweats or a fulminant presentation with fever, altered mental status, and focal neurologic deficits.
- An *Ixodes* tick must be attached to the skin for at least 24 hours to transmit infection with the spirochete *Borrelia burgdorferi*. An attached tick should be pulled out of the skin with a forceps, not smoked out with a match or lighter. Patients frequently report bug bites and are often concerned that these are tick bites. The classic lesion of Lyme disease, erythema migrans, is an erythematous lesion that looks like a target because of its characteristic pattern of concentric pale and red circles. The lesion enlarges day by day typically to more than 5 cm in diameter. The lesion is not painful or pruritic.⁴
- The classic clinical presentation of meningitis due to Lyme disease is fever, headache, meningismus, and photophobia. Patients may have either unilateral or bilateral facial nerve palsy or a painful radiculopathy.

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A radiculitis may be due to herpes simplex virus HSV-2 or *Borrelia burgdorferi*. The infectious etiologies of a clinical syndrome of fever, headache, and cranial nerve abnormalities are fungal meningitis (*Cryptococcus neoformans*, *Histoplasma capsulatum*, *Coccidioides immitis*), tuberculous meningitis, syphilitic meningitis, Lyme disease, and HIV.

- The onset of symptoms of arthropod-borne encephalitis may be preceded by an influenza-like prodrome of fever, malaise, myalgias, nausea, and vomiting. This prodrome is followed by headache, an altered level of consciousness, seizures, and focal neurologic deficits.
- The flaviviruses, which include St. Louis encephalitis virus, West Nile virus, and Japanese encephalitis virus, can cause an encephalitis associated with signs of parkinsonism. The patient that presents with a poliomyelitis-like syndrome with acute asymmetric flaccid weakness may have either an enteroviral infection or infection due to West Nile virus.
- Herpes simplex virus 1 encephalitis is a febrile illness with hemispheric headache, confusion, disorientation, language abnormalities, memory impairment, and seizures. Infection with *Listeria monocytogenes*, enterovirus-71, or HSV-1 may present as rhombencephalitis.
- The classic symptoms of varicella zoster virus encephalitis are headache, fever, confusion, new-onset seizures, and/or focal neurologic signs or symptoms. Ask patients about a history of shingles in the past several months, but don't exclude the possibility of varicella zoster virus encephalitis in the absence of such a history. Typically, varicella zoster virus encephalitis is due to ischemic and hemorrhagic infarctions in both cortical and subcortical gray and white matter; therefore, patients present with an altered level of consciousness, new-onset seizures, or focal neurologic deficits. Zoster reactivation may also cause ventriculitis and periventriculitis with hydrocephalus, and when it does, the patient presents with altered mental status and trouble with gait.
- Rocky Mountain spotted fever due to infection with *Rickettsia rickettsii* presents with fever, headache, altered mental status (stupor, confusion, delirium, coma), seizures, and focal neurologic deficits. A petechial rash is characteristic of Rocky Mountain spotted fever. The rash of Rocky Mountain spotted fever consists initially of 1-to-5-mm pink macules that first appear on the wrists and ankles then spread centrally to the chest, face, and abdomen. Petechial lesions in the axilla and around the ankles accompanied by lesions on the palms and soles of the feet are characteristic of Rocky Mountain spotted fever. After a few days, the macules will turn from pink to dark red to purple. The other infectious diseases during which there may be a rash on the palms and soles are syphilis and meningococcemia.
- Progressive multifocal leukoencephalopathy presents with focal neurologic deficits (often visual field abnormalities, typically homonymous hemianopia) and behavioral or cognitive changes.
- Myoclonus is not the first sign of sporadic Creutzfeldt-Jacob disease. Cognitive decline alone or with ataxia is usually the first sign. When myoclonus develops, the periodic complexes on electroencephalogram (EEG) are often present as well.
- When a patient presents with stroke and fever, the differential diagnosis is infective endocarditis, bacterial meningitis, varicella zoster virus encephalitis, syphilis, tuberculous meningitis, and fungal meningitis.
- Whipple's disease is a clinical syndrome of weight loss, diarrhea, migratory arthralgias, oculomasticatory or orofacial skeletal myorhythmia, vertical gaze palsy, and cognitive changes.
- In the United States, most cases of rabies are due to the bite or saliva of a bat, and patients often are not aware of having been bitten. Ask the patient's family and friends about the possibility of exposure to a bat, including sleeping in a room with an open window that did not have a screen. The incubation period can be as long as 3 months. Rabies due to a bat bite presents with focal neurologic deficits, choreiform movements, myoclonus, seizures, and hallucinations. Phobic spasms are not a cardinal feature of bat rabies.
- For many infectious diseases, an ophthalmological evaluation can be helpful in diagnosis. For example, the ophthalmologist can be very helpful in the evaluation of an immunosuppressed patient with encephalitis with associated cytomegalovirus retinitis or toxoplasmic chorioretinitis.

CEREBROSPINAL FLUID

- The cerebrospinal fluid (CSF) should be examined promptly after it is obtained because white blood cells in the CSF begin to lyse after ~90 minutes. A normal CSF-to-serum glucose ratio is 0.6. A CSF-to-serum glucose ratio of less than 0.31 is seen in ~70% of patients with bacterial meningitis.
- Never send tube #1 for Gram's stain as there is a risk of the fluid being contaminated with the common skin contaminant *Staphylococcus epidermidis* (coagulase-negative staphylococci). This organism appears as gram-positive cocci on Gram's stain. The temptation is strong to send any tube other than #1 for cell count because more red blood cells will appear in tube #1 than in subsequent tubes when the lumbar puncture has been traumatic. Tube #1 can be sent for glucose and protein concentrations.
- There may initially be a predominance of polymorphonuclear leukocytes in the CSF in enteroviral

meningitis and in arthropod-borne viral central nervous system (CNS) infections. In enteroviral meningitis, there is a transition to a lymphocytic pleocytosis within 24 hours. In an arthropod-borne viral infection, the transition to a CSF lymphocytic or mononuclear pleocytosis may take several days.

- Herpes simplex virus 2 is the most common cause of recurrent meningitis, with CSF lymphocytic pleocytosis and a normal glucose concentration. When HSV-2 is the causative agent of meningitis due to reactivation of HSV-2, CSF polymerase chain reaction (PCR) for HSV-2 may not be positive, and the patient may not have a history of genital lesions. Daily prophylactic antiviral therapy for suppression of recurrent HSV-2 infections should be tried for the prevention of recurrent lymphocytic meningitis, even in the absence of a history of genital lesions or a positive CSF PCR for HSV-2. The CSF HSV PCR test may be negative in the first 72 hours of symptoms of HSV-1 encephalitis.
- The CSF glucose concentration is typically only mildly decreased in tuberculous meningitis (35 to 40 mg/dL). The CSF 14-3-3 test is similar to many rheumatological tests in that it only adds fog to the

clinical picture. Cerebrospinal fluid 14-3-3 false-positive results have been reported in HSV encephalitis, recent cerebral infarction, degenerative dementias (including Alzheimer's disease), carcinomatous meningitis, and anoxic encephalopathy. The CSF angiotensin-converting enzyme (ACE) is insensitive, and elevated values are nonspecific.

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