Myth: Cerebrospinal fluid analysis can differentiate bacterial meningitis from aseptic meningitis

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Despite increasing use of the *Haemophilus influenzae* and pneumococcal vaccines, acute bacterial meningitis is a serious cause of mortality and morbidity worldwide. Evaluation of patients with meningitis is complicated by the fact that clinical findings do not reliably differentiate bacterial meningitis from other illnesses such as aseptic (viral) meningitis. This is particularly true in young children and infants, making diagnosis in the pediatric age group especially problematic. There is a prevalent myth that cerebrospinal fluid (CSF) white cell counts and other surrogate markers are reliable indicators of bacterial versus viral infections. This is a dangerous misconception.

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Prompt treatment of bacterial meningitis with antibiotics administered intravenously (IV) is crucial in order to reduce disastrous consequences, particularly neurological dysfunction and death. Failure to promptly diagnose and treat bacterial meningitis is consistently listed among the most significant medicolegal risks for physicians. In contrast, patients with aseptic meningitis do not require antibiotics and rarely require hospitalization unless comorbidity or illness severity dictate otherwise. A reliable means of distinguishing between bacterial and viral central nervous system (CNS) infections would reduce the risk and expense of unnecessary antibiotic therapy and hospitalization in aseptic meningitis patients.

The most important diagnostic study for patients with possible meningitis is lumbar puncture with CSF analysis. The gold standard for diagnosing bacterial meningitis is the CSF culture, despite its limited value in patients who have been partially treated. However, physicians must make treatment decisions before culture results are available, and they depend on CSF findings such as cell count, glucose, protein, and Gram's staining to help them do so.

Traditional teaching is that, in patients with bacterial meningitis, CSF white blood cell (WBC) counts are at least 300–2000 cells/mm^3 (often closer to 10 000) and CSF protein levels are above 150 mg/dL (>1.5 g/L). At the same time, CSF glucose concentration is expected to be below 40 mg/dL (<2.5 mmol/L), with a CSF:serum ratio of <0.25. Conversely, aseptic meningitis is reportedly characterized by CSF WBC counts of fewer than 200 cells/mm^3, normal or slightly decreased glucose concentration, and protein levels of 50–200 mg/dL (0.5–2.0 g/L).[1] Gram's stains of spinal fluid are virtually diagnostic of bacterial meningitis when microorganisms are seen, but negative results of initial Gram's staining do not exclude the diagnosis.

Several authors have demonstrated, however, that the CSF leukocyte count cannot reliably distinguish between bacterial and aseptic meningitis.[2,3] For example, Levy and colleagues[4] studied 650 children evaluated for meningitis, of whom 50 had bacterial meningitis and 212 had aseptic meningitis. Patients with bacterial meningitis exhibited a

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wide range of CSF values for WBC, glucose and protein, and these values overlapped significantly those of the aseptic meningitis group, rendering a diagnosis based on any one CSF parameter unreliable.

Traditional teaching also holds that bacterial meningitis is associated with polymorphonuclear (PMN) leukocyte predominance and aseptic meningitis with mononuclear leukocyte predominance in the CSF. Negrini and colleagues[5] reviewed 158 patients with meningitis and found that most of those with aseptic meningitis had a PMN predominance where neutrophils and juvenile forms accounted for >50% of CSF leukocytes. It is often said that polymorphs may predominate during the first 24 hours of aseptic meningitis, but these authors found that they predominated well beyond this period and that even higher proportions of CSF PMNs (up to 90%) were not specific for bacterial meningitis. PMN leukocyte predominance therefore does not distinguish bacterial from aseptic meningitis.

Other CSF studies have been advocated as a means of distinguishing bacterial from aseptic meningitis. These include CSF leukocyte aggregation,[6] CSF lactate[7] and CSF cytokine levels, among others. Many authors have studied these tests, but have not conclusively demonstrated their utility. Bacterial antigen studies, more widely used, also have limited utility during the initial patient encounter.

Because no single laboratory value differentiates bacterial and aseptic meningitis, several authors have proposed multivariable approaches. These combine CSF analysis with parameters such as serum laboratory values, patient age and month of presentation. Jaeger and colleagues[8] developed a model with high (97.1%) negative predictive value for bacterial meningitis in children under 3 years old, but caution that the model should be used as only one piece of diagnostic information and not as the sole basis for diagnosis. To complicate matters, most cases of bacterial meningitis in this and other previous studies were caused by *H. influenzae*, now rare in areas with widespread *H. influenzae* vaccination. To date, no single diagnostic model has been validated in an adequate sample of patients as anything more than an adjunct to physician judgement.

Enteroviruses are reported to be the most common cause of aseptic meningitis in North America. Viral CSF cultures can reliably diagnose these infections, but are subject to the same prolonged turnaround times as bacterial cultures. Tests that more rapidly detect CSF enteroviral infection could confirm aseptic meningitis and prevent unnecessary investigations and hospitalization. Ramers and colleagues[9] suggest that an enterovirus-specific reverse transcriptase polymerase chain reaction (PCR) assay may provide the answer. In hospitalized patients this test had a sensitivity and specificity approaching 100% — sufficient to guide decision-making and improve diagnostic and therapeutic choices. Although it is not yet widely available, nor rapid enough to drive immediate decisions in the emergency department, PCR testing may become an important diagnostic tool in the future.

Acute bacterial meningitis causes devastating morbidity and mortality if not treated rapidly and appropriately. There is considerable overlap in CSF diagnostic parameters for bacterial and aseptic meningitis, and even multivariable diagnostic models are not foolproof. Physicians must proceed with caution when using CSF analysis to differentiate the two illnesses.

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