**INTRODUCTION**

The mortality rate of infectious meningitis continues to be alarmingly high despite the availability of antibiotics. With widespread use of *Haemophilus influenzae* type B vaccinations in the past two decades, the overall rate of infectious meningitis, especially in the pediatric population, has significantly declined. Nonetheless, bacterial meningitis remains a public health concern with estimated mortality rates of 17-25%.1,2

The following article is based on a case of *Listeria monocytogenes* meningitis and encephalitis seen at the start of 2006. A general discussion on the clinical features of acute meningitis is provided. In addition, the epidemiology and mechanism of disease of this unique pathogen are addressed.

**THE CASE**

Mrs. G, a 57 year-old woman, was brought into the ER by her husband in early January, with a 7-day history of lumbar back pain, radiating to the occiput, so significant she could not ambulate. She also reported having a very severe headache, exacerbated by loud noise or speech, a three-day history of vomiting, photophobia and extreme weakness. On presentation, Mrs. G. was febrile, unable to answer simple questions, and had difficulty following directions during the history and physical examination. Inquiry into past medical history revealed osteoarthritis, GERD, a remote history of vertebral fracture and laminectomy with residual chronic back pain. She had no significant history of infections, and was not known to be immune compromised. Mrs. G. lived in a house with her husband and children, had no recent travel, no sick contacts, and had not eaten anything new or unusual.

What is the Differential Diagnosis Based on this Patient’s History?

There are several possible underlying etiologies for an acute change in mental status, otherwise referred to as an acute confusional state. These can be categorized as vascular, drug-induced, infectious, autoimmune, neoplastic, seizure, metabolic disorders, or electrolyte disorders.3 Possible vascular causes are subarachnoid hemorrhage, which can present with severe “thunder-clap” headache and signs of meningismus, or cerebral vascular accidents such as stroke and transient ischemic attacks. Alcohol intoxication, withdrawal (delirium tremens), or other drug intoxication states (e.g., due to narcotics) must also be considered. Infectious causes such as meningitis, encephalitis, pulmonary infections or urinary tract infections may all lead to acute changes in mental status. However, the latter two are more likely to cause delirium in elderly patients, while CNS infections may lead to acute confusional states in all age groups. In order to narrow down the differential diagnosis,
further information is needed from physical exam and investigations.

**CLINICAL ASSESSMENT OF ACUTE BACTERIAL MENINGITIS**

Given the generally serious nature of the disease, it is important to be able to clinically assess the pre-test probability of infectious meningitis. An article published as part of JAMA’s series on *The Rational Clinical Exam*, provides an evidence-based approach to history-taking and physical examination of a patient suspected of having acute meningitis. The presence of nausea and vomiting, headache and neck pain on patient history were analyzed in order to assess the sensitivity of these symptoms in detecting the presence of meningitis. A literature review was conducted, and a meta-analysis performed on several chart reviews and one prospective trial that dealt with this topic (Table 1). The specificities of many of these signs and symptoms were not discussed; however, it is intuitive that as the sensitivities approach 100%, the specificities are often lower. For example, fever is a general sign that may be seen in many different pathologic conditions.

<table>
<thead>
<tr>
<th>Sign/Symptom</th>
<th>Pooled Sensitivity (95% Confidence Interval)</th>
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<tbody>
<tr>
<td>Neck pain</td>
<td>28%*</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>30% (22-38%)</td>
</tr>
<tr>
<td>Fever</td>
<td>85% (78-91%)</td>
</tr>
<tr>
<td>Neck Stiffness</td>
<td>70% (58-82%)</td>
</tr>
<tr>
<td>Altered Mental Status</td>
<td>67% (52-82%)</td>
</tr>
<tr>
<td>Jolt Accentuation</td>
<td>97%*</td>
</tr>
<tr>
<td>Generalized Headache</td>
<td>50% (32-68%)</td>
</tr>
</tbody>
</table>

*Assessed by only one study

This article indicated that physical examination plays a much bigger role in diagnosis. Interestingly, the classic clinical triad of fever, nuchal rigidity and change in mental status was studied in three reviews, and found to have a pooled sensitivity of only 46% (95% CI, 22%-69%) [n=426]. However, the majority (95%) of patients were found to have at least two of these three clinical findings, indicating that infectious meningitis can be confidently ruled out in the absence of all three components in the triad. The presence of focal neurological signs, rash, or positive Kernig’s or Brudzinski’s signs all had relatively low sensitivities. However, the jolt accentuation test, in which a patient is asked to rotate his/her head to a 90-degree angle on each side at a rate of 2-3 rotations per second and then asked to report if there is a worsening of the baseline headache, has a sensitivity of 97% and specificity of 60%, demonstrating the clinical value of this simple test.

**THE CASE: PHYSICAL EXAMINATION**

The patient was found to be hemodynamically stable, and there were no abnormal findings on cardiovascular and respiratory examination. When asked to perform the jolt accentuation test, the patient complained of severe neck pain and worsening of her headache. Neck flexion was limited to roughly 20 degrees due to pain. The patient was not willing to cooperate in Kernig and Brudzinski maneuvers, and these exam techniques were thought to be redundant given the presence of the other signs and symptoms. Cranial nerve exam revealed evidence of saccadic movements, coarse nystagmus on extreme lateral gaze in both directions, and blurred vision and diplopia in the right eye at all extremes of gaze. Also, the trigeminal nerve exam elicited numbness on the right side of her face in all three branches. Muscle power testing was essentially normal except for global weakness, which was thought to be secondary to the illness and a general deconditioned state. Testing for sensation (including light touch and vibration), reflexes, tone, and cerebellar examination were all within normal limits.

Given these clinical findings, a lumbar puncture was performed, and the patient was provided with empiric meningitis treatment: intravenous cefotaxime and vancomycin, along with adjuvant dexamethasone therapy.

**THE CASE: DIAGNOSTIC AND LABORATORY INVESTIGATIONS**

In Mrs. G’s case, the spinal fluid glucose levels, protein concentrations and leukocyte counts and differential were all consistent with bacterial meningitis. CSF obtained from lumbar puncture revealed gram-positive bacilli on staining, and fluid culture confirmed *Listeria monocytogenes* infection.

A CT scan of the head was unremarkable. Due to the patient’s persistent complaints of headache and double
vision, an MRI of the head was performed in an attempt to understand the source of these symptoms (Figure 1). There was no evidence of meningeal enhancement or intraparenchymal abscess. However, T2-weighted signal intensity revealed a focus of hyperintensity at the junction of the right pons and cerebellum, consistent with a focus of encephalitis in the right cerebellar peduncle, the expected area of the trigeminal nerve (CN V) nucleus, and in close proximity to the abducens nerve (CNVI) nucleus. Visual evoked potentials were performed and found to be near the upper limit of normal, with slight delays in the right eye compared to the left.

**EPIDEMIOLOGY PATHOGENESIS AND MANAGEMENT OF LISTERIA MONOCYTOGENES INFECTION**

*Listeria monocytogenes* is a gram-positive bacillus. This facultative anaerobe is ubiquitous organism that can be easily isolated from the environment (e.g., soil, dust, fertilizer, decaying plant life and sewage).6 It is also found in the lower gastrointestinal tracts of animals and is a common veterinary pathogen. *Listeria* has received some press attention in past years because of gastroenteritis outbreaks associated with the consumption of processed meats, such as lunch meats and precooked seafood, and dairy products.6,7,8,11 This pathogen has been estimated to be responsible for 1-3% of cases of infectious meningitis in North America. Incidence rates of *Listeria* meningitis have been reported to be 1 to 2 per million in North America, and the case fatality rates, at 15-40%, are most similar to those of *Streptococcus pneumoniae*.

Listeriosis may manifest as a self-limited gastroenteritis, as a more severe CNS infection (meningitis, encephalitis, abscess), or occasionally as endocarditis. Meningitis and encephalitis are typically seen only in immunocompromised hosts, neonates and elderly patients.6,10 In pregnant women, Listeriosis usually presents as a flu-like illness during the third trimester of pregnancy, when cell-mediated immunity is most compromised. Although CNS infections are not common in pregnancy, listeriosis can result in preterm labor and complications with the fetus can include abortion, stillbirth, and even granulomatosis infantisepi-ca.6,10

By understanding the peculiar lifecycle and mechanism of disease exhibited by *Listeria monocytogenes*, further insight into the clinical manifestations and treatment of this organism can be achieved. *L. monocytogenes* is phagocytosed by macrophages and becomes enclosed in the highly acidic phagolysosome, which is fatal to most bacteria. However, in response to the low pH, *Listeria* organisms release an exotoxin, listeriolysin O, that promptly lysed the membrane of the phagolysosome and allows for invasion into the cytoplasm.6 In the cytoplasm, *L. monocytogenes* organisms proliferate, with a doubling time of approximately one hour, and within two hours, they migrate to one end of the host cell. Cellular protrusions known as filopods are pushed through the host cell’s membrane, allowing for their recognition and phagocytosis by adjacent cells, where the life cycle begins anew.6

It is speculated that *L. monocytogenes* uses actin filaments from the host cell’s cytoskeleton to form a “tail” that aids in the organism’s intracellular motility. The molecular model of this actin tail formation is beyond the scope of this article, but can be found in other sources.6

As can be seen from the above discussion, the lifecycle of *Listeria monocytogenes* is predominantly intracellular. Therefore, cell-mediated immunity serves as the primary defense, whereas, humoral immunity plays a limited role. Thus, patients with impaired cell-mediated immunity, such as individuals with AIDS,6 patients on corticosteroid therapy, and women in the third-trimester of pregnancy, are at higher risk of listeriosis.

Treatment regimens must incorporate antibiotics that can effectively penetrate cell membranes. Previous recommendations of combining an aminoglycoside (e.g., gentamicin) with ampicillin, have proven to be ineffective,6 although some clinicians still prefer this combination as a first-line therapy.12 The poor cellular penetrability of ampicillin and aminoglycosides are reasonable explanations for the slow response to these drugs. Current recommendations include using trimethoprim-sulfamethoxazole (TMP-SMX), which is a drug that easily enters cells and is effective in killing listeria.6 Some experts also recommend using ampicillin in addition to TMP-SMX, which appears to have synergistic effects. However, there is no universally accepted treatment protocol for listeria meningitis.12

**THE CASE: PATIENT OUTCOME**

Mrs. G. received intravenous treatment with TMP-SMX for a total of 14 days. She continued to make progress throughout her stay and prior to discharge, began ambulating on her own. The photophobia, nausea and vomiting were completely resolved, and her headache was greatly improved. Signs of global muscular weakness remained, and in fact, may have been exacerbated by the initial lack of mobility. Some residual focal neurological signs remained including coarse nystagmus and reduced sensation to pinprick on the right side of her face. The patient was sent home with a recommendation for follow up by her family physician, as well as a future MRI scan to monitor the progress of the focal area of infection in the cerebellar/pontine area.

**CONCLUSION**

This case is atypical in that Listeria was an unlikely pathogen in this young and generally healthy host. Focal neurological signs are also uncommon in bacterial meningitis. Despite the peculiarities in the case presentation, the patient presented with some of the dogmatic features of infectious meningitis, including the triad of fever, neck stiffness and altered mental status. By using an evidence-based assessment, clinicians may be able to approach suspected cases of infectious meningitis with more certainty and direc-
tion. Furthermore, an understanding of the pathogenesis of Listeria monocytogenes allows clinicians to select an effective management protocol for this potentially life-threatening disease.

REFERENCES

Author Biography
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