

BRIEF CASE**A Classic “Not to be Missed”**

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THE CASE

Mrs. W, a 36 year old woman who lives with her husband and two children, was recently brought in to an emergency department in Florida while on vacation with her family. She presented acutely with pain in her left ear, garbled speech, and an inability to answer simple questions and follow commands. Past medical history from her family revealed she has asthma for which she uses a fluticasone/salmeterol inhaler, and has been a daily pack-and-a-half smoker for 20 years. Review of systems was unremarkable except that Mrs. W had suffered from a left inner ear infection three weeks earlier, for which her family doctor had prescribed ampicillin drops. This seemed to have resolved prior to the vacation.

What may have caused the acute change in mental status?

When assessing altered level of consciousness, it is possible, on history alone, to generate a working diagnosis. The list of differentials in this case includes substance-related causes such as alcohol intoxication or withdrawal (delirium tremens), as well as drug use or overdose.¹ Metabolic imbalances (hypoglycemia, uremia, hypoxia, hypercapnea), electrolyte disturbances (hyponatremia, hypernatremia, hypercalcemia), and endocrinologic abnormalities (Addison's disease, hypothyroidism) can all manifest as confusion. Hypothermia, hyperthermia, hypotension, hypertensive encephalopathy, and ischemia are further confounders. Also included are intracranial space-occupying lesions such as hemorrhage (intracranial, subarachnoid, subdural, or epidural) and neoplasms. Infectious processes such as sepsis, brain abscess, bacterial or aseptic meningitis, and encephalitis cause marked changes in mental status. Less commonly presenting in this manner are lung and urinary tract infections. Episodes of mania and major depression are examples of psychiatric conditions to keep in mind when faced with acute confusion.

Mrs. W's recent left inner ear infection and presentation

with marked left ear pain brings an infectious process to the top of the list. History alone allows limited further problem-solving. The acute nature of her presentation and relatively unremarkable past medical history rule out more slowly-evolving processes such as neoplasm, and a history lacking head trauma in a healthy 36-year-old woman makes intracranial hemorrhage less likely.

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Physical examination revealed a fever of 40.7°C, blood pressure of 111/67, pulse rate of 103, respiratory rate 20, and oxygen saturation on room air of 100%. She was alert at first, but disoriented with inappropriate answers. She subsequently developed aphasia and apraxia. No lymphadenopathy was found. Petechiae were absent. The neck was stiff with meningismus – Brudzinski and Kernig signs were positive. Neurological examination was questionable for impairment of right hand movements. Empiric ampicillin 2g IV q4h was started based on clinical suspicion of bacterial meningitis.

How useful are the clinical signs of bacterial meningitis?

High grade fever and signs of meningeal inflammation narrow the focus to meningitis. Clinical features of acute meningitis can be attributed to its pathophysiology. Systemic infection accounts for fever, myalgias, and petechial rash caused by septic emboli. Meningeal inflammation explains nuchal rigidity and positive Brudzinsky's and Kernig's signs (Figure 1) – protective reflexes to prevent stretching of the inflamed and hypersensitive nerve roots.^{3,4} Inflammation further explains headache and cranial nerve palsies. Cerebral vasculitis may ensue, causing cerebral edema, elevated intracranial pressure (ICP) with subsequent change in mental status, vomiting, further focal neurologic deficits, and seizures. Although the classic triad for acute meningitis consists of fever, neck stiffness, and

altered mental state, less than two thirds of patients manifest all three⁵. As a general rule, absence of all three of these clinical signs virtually eliminates the diagnosis of meningitis.

Although Brudzinsky's and Kernig's signs have not been well studied, it has been shown that they are of low sensitivity but of high specificity for acute meningitis.⁶ Another test which seems to have high sensitivity is jolt accentuation of headache described by Uchihara and Tsukagoshi,⁷ elicited by asking the patient to turn his or her head horizontally at a frequency of 2 to 3 rotations per second. Worsening of a baseline headache represents a positive sign.

Still remaining to be considered in the febrile, confused patient with meningismus, however, is viral encephalitis. Mrs. W. presented with the classic triad of meningitis, as well as having highly specific signs of acute meningitis. Once suspected on clinical grounds, cerebrospinal fluid (CSF) is evaluated to make a definitive diagnosis.

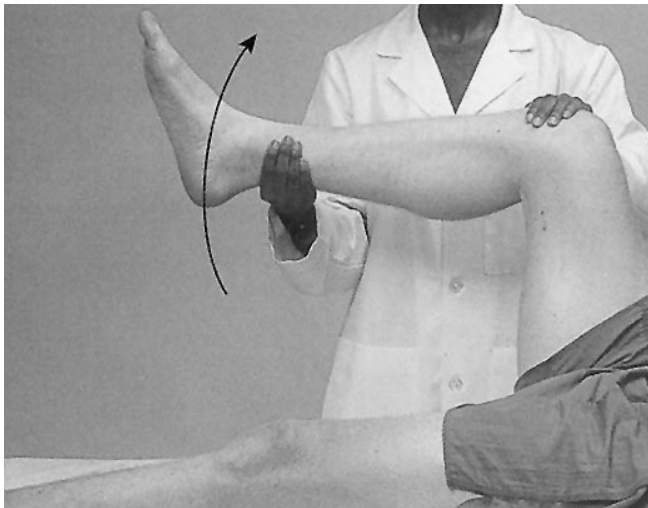


Figure 1. Kernig's Sign. Pain and increased resistance to extending the knee are a positive Kernig's sign. When bilateral, it suggests meningeal irritation.

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Notable on basic panel were a leukocyte (WBC) count of $17.6 \times 10^9/L$ with 93% neutrophils. Her serum glucose was 3.38 mmol/L. The patient underwent lumbar puncture (LP) for CSF analysis (Table 1).

Table 1. The patient's lumbar puncture results

Appearance	cloudy, xanthochromic
WBC	2772/mm ³
Neutrophils	96%
monocytes	4%
RBC	54/mm ³
CSF protein	1.71 g/L
CSF glucose	1.6 mmol/L
Opening Pressure	not documented

CSF Gram stain and culture were negative. Blood cultures were negative. Antigen testing for *Haemophilus influenzae*, *Neisseria meningitidis*, and *Streptococcus pneumoniae* were also negative. Computed tomography (CT) of the brain without contrast was normal.

How are the Lumbar Puncture results interpreted?

Normal CSF is clear and colourless, and contains about 0.2-0.5 g/L protein, which does not cross the blood brain barrier (BBB) due to its molecular size. Normal CSF glucose is approximately 40% of that in the serum. There are less than 6 cells/mm³, all lymphocytes, and opening pressure is 100-200 mmHg. Pleocytosis of the CSF indicates an increase in the WBC count or protein level, indicating an infectious or inflammatory process. CSF is most useful in differentiating between acute bacterial and viral meningitis. Bacterial meningitis is indicated by a WBC count of 100-5000/mm³, with a predominance of neutrophils (>80%). Viral or aseptic meningitis may have an elevated cell count, but only mildly at 10-100 /mm³, with lymphocytes predominating. Protein concentration in bacterial meningitis is greater than 1.0 g/L, but will be only mildly elevated in viral, if at all. Also useful is the ratio of CSF:serum glucose. Bacteria present in the CSF consume glucose to decrease the ratio to less than 0.3. Non-bacterial meningitis has a ratio of 0.6 or greater.⁸ Opening pressure may be elevated to greater than 200 mmHg with a bacterial etiology. Mrs. W has a CSF profile fitting that of acute bacterial meningitis.

What are the bugs and how often are they detected?

Since the introduction of the *Hemophilus B* conjugate vaccine (HiB), *S. pneumoniae* has become the primary causative organism of bacterial meningitis in North American adults over the age of 20. It is followed closely by *N. meningitidis*, and now more distantly by *H. influenzae* (Table 2). Colonization of the nasopharynx by *S. pneu-*

Table 2.

Epidemiology of organisms causing bacterial meningitis in North America.

Bacterium	Causative Organism (% cases)	Incidence (per 100 000)	Case-Fatality Rate (%)
<i>Streptococcus pneumoniae</i>	30-50	0.6-1.2	19-46
<i>Neisseria meningitidis</i>	15-40	0.5-1	3-17
<i>Haemophilus influenzae</i>	2-7	<1	3-11
<i>Listeria monocytogenes</i>	1-3	0.1-0.2	15-40
Other bacteria	<5	Not available	Not available

Adapted from: Bacterial meningitis in children and adults—changes in community-acquired disease may affect patient care.⁹

moniae provides a source of meningeal spread from infections such as sinusitis and mastoiditis. Incidence of penicillin-resistant pneumococcus is increasing, and case-fatality rates remain high (up to 45%). A high index of suspicion is necessary. CSF Gram stains reveal bacteria in about 50-80% of cases and cultures are positive in at least 85% of cases.⁹ However, sensitivity of both tests decreases to 50% in patients treated empirically with antibiotics. Blood cultures should always be done, as they may uncover a pathogen the CSF could not. CSF antigen detection tests for the bacterial pathogens most commonly involved in meningitis have good specificity, but sensitivity is no bet-

ter than that of a Gram stain.⁹ Ruling out bacterial meningitis therefore cannot be based on negative results. Mrs. W's negative gram stain, negative blood and CSF cultures and uninformative antigen tests, although unhelpful in pinpointing a specific pathogen, could not rule out a bacterial etiology for her meningitis. This is particularly true considering she received empirical ampicillin treatment.

To CT or not to CT?

In general, imaging studies of the head often delay diagnosis and treatment of meningitis, and thus should be reserved for patients with evidence of raised ICP and mass

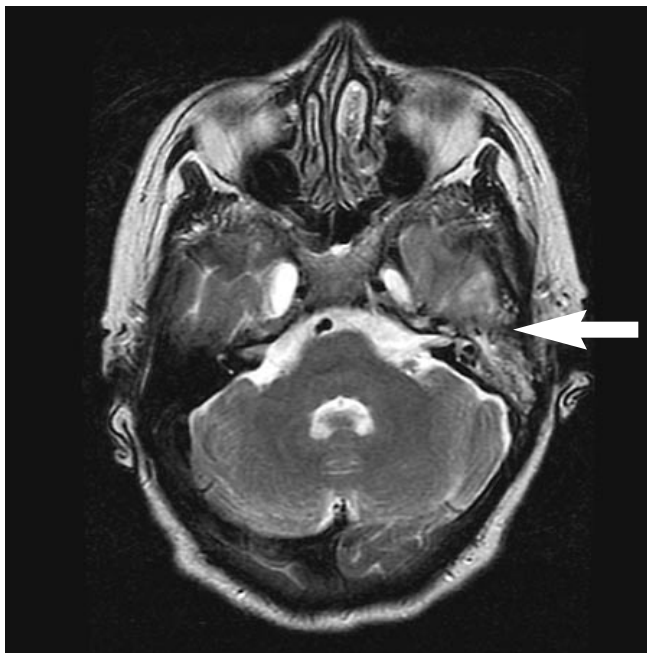


Figure 2. Axial FSE T2-weighted MRI of the head. The solid arrow shows left-sided mastoiditis extending to the inferior temporal lobe of the brain.

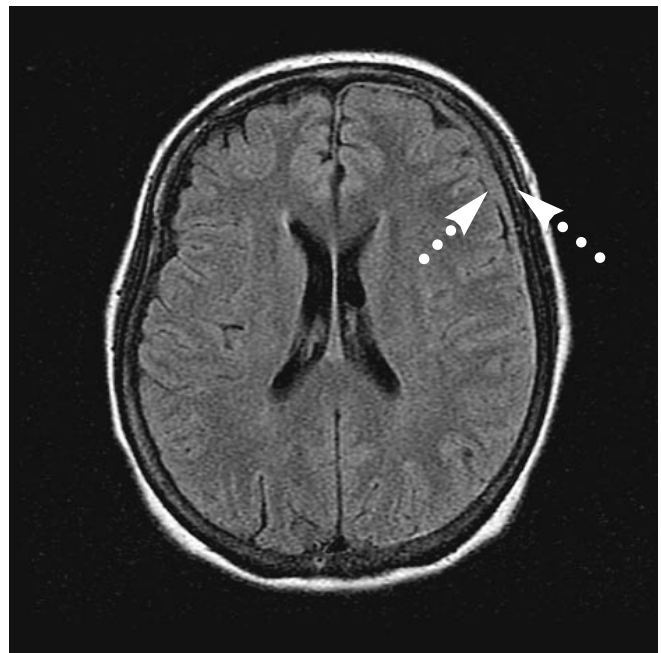


Figure 3. Axial T2-weighted FLAIR MRI of the head. The dashed arrows delineate a left-sided inflammation of the dura and arachnoid matter indicating meningitis.

effect, such as papilledema, seizures, or focal neurological signs.¹⁰ CT may be useful in detecting local sources of infection (mastoid or sinus) or alternate pathology (brain abscess, venous sinus thrombosis, infarct), but lacks the resolution of magnetic resonance imaging (MRI) for viewing neural structures such as the meninges.

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Mrs. W was isolated and given dexamethasone 8 mg IV q12h. Ceftriaxone 2 g IV q12h and vancomycin 1g IV q12h were added to the ampicillin. Dexamethasone and ampicillin were subsequently discontinued. Acyclovir 500 mg IV q8h was added, with phenytoin and lorazepam as needed for seizure activity, of which she had none.

Is the treatment appropriate?

The use of corticosteroid therapy for reducing inflammation and edema in bacterial meningitis has been a matter of debate. A recent randomized controlled trial showed that early adjunctive treatment with dexamethasone significantly reduced the risks of both unfavourable outcomes and death in cases of pneumococcal meningitis, and may be applicable to cases with other bacterial etiologies.¹¹ Our patient's recent inner ear infection and painful ear on presentation suggest that infection of the inner ear with pneumococcus subsequently extended to the adjacent mastoid air cells and meninges. Unsuccessful treatment with ampicillin drops for the ear infection may also suggest that the responsible pathogen has developed penicillin resistance. In such cases, a combination of vancomycin and a third generation cephalosporin such as cefotaxime or ceftriaxone will avoid resistance, and ensure both gram-positive coverage and penetration of the BBB. Many of the drugs used to treat meningitis depend on the compromised state of the BBB in order to cross it. Dexamethasone, therefore, may inhibit the absorption of these drugs after its acute-phase benefits. It was therefore discontinued in this case, considering also the absence of cerebral edema on CT. The uncertainty surrounding Mrs. W's neurological examination and disproportionately severe delirium throughout her course in hospital prompted the addition of acyclovir to treat the less likely involvement of viral encephalitis. CT with contrast or T2-weighted MRI images would help to exclude this possibility.

RESOLUTION

Mrs. W began to respond and was flown back to Canada for further treatment. Confusion and inability to understand and execute appropriate speech persisted, despite resolution of her fever and leukocytosis. This steadily improved over the following week during which a MRI of her brain showed a resolving left-sided mastoiditis and meningitis (Figures 2 and 3), with no evidence of encephalitis. The acyclovir was discontinued and the patient was sent home on oral antibiotics. †

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Jennifer Robinson is a medical student in her final year at McMaster University.

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