

CHAPTER 32

THE MAN WITH HEADACHE AND FEVER

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Case History

This 72-year-old man had an abrupt onset of rigors followed by fever late one evening. When seen by his family physician the next day he also complained of myalgia. Apart from the fever, his physical examination was unremarkable. Acetaminophen was prescribed for the fever and the myalgia.

Three days later at about 8 AM, he complained of severe headache and stiffness of the neck. Over the next 2 to 3 hours he became progressively confused and was brought to the emergency room by his family.

On examination he was acutely ill; his oral temperature was 39°C, he was arousable but did not respond to most questions. There was nuchal rigidity and crackles were heard on auscultation over the right side of his chest anteriorly and laterally.

Ceftriaxone, 2 gm every 12 hours intravenously, and ampicillin, 2 gm every 6 hours intravenously, were administered. A lumbar puncture (LP) revealed an opening pressure of greater than 500 mm H₂O. The cerebrospinal fluid (CSF) was cloudy and had a protein concentration of 2827 mg per deciliter, and a glucose concentration of 0 mg per deciliter; the white blood cell count was 425 cells per cubic millimeter of which 81% were polymorphonuclear leukocytes. A Gram's stain of a centrifuged specimen of CSF showed many polymorphonuclear leukocytes and gram-positive diplococci. At this point ampicillin was discontinued and vancomycin, 1 gm every 12 hours intravenously, was added to the ceftriaxone.

A computed tomography (CT) scan of his head showed atrophy consistent with his age, left mastoidectomy, and opacification of the mastoid air cells on the right.

The next day both blood and cerebrospinal fluid cultures were positive for *Streptococcus pneumoniae*. The pneumococcus was susceptible to penicillin with a minimal inhibitory concentration (MIC) of 0.016 µg per milliliter.

Over the first 48 hours in hospital he became afebrile. When the results of the susceptibility tests were known, antibiotic therapy was changed to penicillin, 4 million units every 4 hours intravenously.

By day 5 he was responding to comments and indicated that he still had a headache. He slowly improved and by day 11 he was headache free; antibiotics were discontinued on day 14 and he was transferred to a rehabilitation facility on day 21.

Questions about This Case

- Why are the characteristics of the headache so poorly described in this case?
- Describe the characteristics of the headache caused by bacterial meningitis.
- What is the management of headache associated with bacterial meningitis?
- How long does headache due to bacterial meningitis persist?
- Outline the pathophysiology of headache due to bacterial meningitis.

Case Discussion

The characteristics of the headache are poorly described in this patient for several reasons.

It was evident that the patient was seriously ill with a life-threatening disease. His physicians quickly decided that the headache was not the problem and they focused

(as they should) on immediate therapeutic and diagnostic procedures since it was evident that the most likely diagnosis was bacterial meningitis. Time is of the essence in the management of bacterial meningitis. The median time from arrival in the emergency room until the administration of antibiotics was 2 hours (interquartile range 1.25 to 3.33 hours) for 93 children with bacterial meningitis who were studied from 1987 to 1989. Indeed only one child received antibiotics within 30 minutes of presentation.

The second reason for the poor description of the characteristics of the headache was the mental status of our patient. He was confused and not able to provide detailed answers to any questions. A review of 493 episodes of acute bacterial meningitis in adults found that 51% were confused or lethargic on presentation, 22% were responsive only to pain, and 6% were unresponsive to all stimuli. Only 22% were alert.

The third reason is the age of our patient. In one study only 46% of 48 patients over 60 years of age with bacterial meningitis complained of headache; other studies quote figures as low as 21%. Comparisons of the features of meningitis in the elderly with those in younger patients have shown that older patients are more likely (statistically significantly so) to have a higher incidence of severe mental status abnormalities and to have concurrent pneumonia than younger adults.

The final reason for the poor description of this patient's headache was that the physicians involved in his management included an emergency room physician, an intensivist and an infectious diseases physician. A neurologist surely would have described this headache much better!

Characteristics of the Headache Caused by Bacterial Meningitis

Maybe a neurologist would not have done much better with our patient. A review of the literature on bacterial meningitis in adults reveals that headache due to bacterial meningitis is poorly described. In most instances only the percentage of patients with headache is given. Some authors state that a distinctive feature of headache seen in bacterial and viral meningitis is the retro-orbital component which is markedly exacerbated by the slightest motion of the eyes. In the experience of one of us (TJM) this occurs in aseptic meningitis and is uncommon in bacterial meningitis. Furthermore this phenomenon is also seen in optic neuritis and with idiopathic vascular headaches.

Our patient's presentation is instructive in dissecting the features of headache due to meningitis—especially if it is combined with an overview of the presentation of other patients with meningitis. This 72-year-old man

developed pneumococcal pneumonia and then his meninges and right mastoid air cells were infected as a result of pneumococcal bacteremia. The initial fever and myalgia represent his response to the pneumonia. Interestingly in our study of 2287 adults with community-acquired pneumonia we found that 64.1% of the 944 outpatients and 44.1% of the 1343 inpatients had headache as one of their symptoms. Thus, many patients with meningitis will initially have a headache as part of the nonspecific manifestations of the infection that led to the meningitis, be it pneumonia, sinusitis, mastoiditis, or endocarditis. At this stage myalgia accompanied by a dull throbbing generalized headache of moderate intensity is common. For those patients in whom the sinus, ear, or mastoid is the focus of infection leading to meningitis, headache due to inflammation of these structures is also present. Only 25% of 225 adults with community-acquired meningitis had no predisposing factors that could lead to this infection. The most common predisposing factors were—acute otitis media, 19%, pneumonia, 15%, sinusitis, 12%, endocarditis, 7%, chronic otitis media, 7%, recent head injury, 5%, previous head injury, 4%, diabetes mellitus, 10%, alcoholism, 18%, altered immune state, 19%, cerebrospinal fluid leak, 8%, and an implanted neurosurgical device, 1%.

Perhaps the best setting in which to gain an understanding of the features of headache in bacterial meningitis is in the setting of *Neisseria meningitidis* infection in a young adult. Even here there are two distinct presentations, that of fulminant meningococcemia and the other which is dominated by meningitis. In the former, a previously healthy young adult (often 16 to 25 years of age) has a sudden onset of chills, fever, myalgia, and headache. The headache is usually dull and not the dominant feature. Within 4 to 12 hours this “flu-like” illness has evolved so that the individual is now hypotensive, has multiple petechial hemorrhages, and may be stuporous. In these patients the picture is that of fulminant sepsis and clinical meningitis may not be present. However, if therapy is successful in prolonging or saving life, it is evident that the meninges have been infected. In patients with meningococcal disease in whom the meningitis predominates, headache is a dominant feature. In our study of 51 patients with group C meningococcal meningitis, whose mean age was 13.6 ± 12.9 years, 51% had headache. However, 49% had purpura and fell into the fulminant meningococcemia category—thus most of those with the meningitis presentation had headache (10% had photophobia). This headache starts as part of the infection prodrome as a dull headache but over 2 to 24 hours it becomes intense and changes its character to that of a throbbing generalized headache made worse by head movements, coughing, and straining.

Management of Headache Associated with Bacterial Meningitis

This is the simplest form of headache to deal with—treat the meningitis. The major (and frequent mistake) is delay in administering antibiotics. During an outbreak of meningitis in the U.K., children who were suspected to have meningitis when seen in the physician's office and who were given intramuscular penicillin and sent to hospital had a much better outcome than those who were sent to hospital without antibiotic therapy.

For the optimal treatment of (headache associated with) meningitis do the following:

1. Blood cultures
2. Intravenous antibiotics should be administered within 30 minutes of arrival in ER (choice of antibiotics depends on the age of the patient and the local epidemiology, e.g., the presence of penicillin resistant *Streptococcus pneumoniae*). In most instances of meningitis in adults, ampicillin and ceftriaxone represent reasonable empiric therapy. Remember cephalosporins are not effective against *Listeria monocytogenes* which is the third or fourth most common cause of meningitis in this age group. In a review of 253 adults with community-acquired meningitis, *Streptococcus pneumoniae* accounted for 38%, *Neisseria meningitidis* 14%, *Listeria monocytogenes* 11%, streptococci 7%, *Staphylococcus aureus* 5%, *Haemophilus influenzae* 4%, mixed bacterial species 2%, and 13% were culture negative. Once a pathogen is isolated, therapy can be changed to more specific antibiotics based upon susceptibility studies. This is not a chapter on the treatment of meningitis but remember to give antibiotics intravenously for at least 10 days—never switch to therapy by mouth—most antibiotics are not sufficiently absorbed through the gastrointestinal tract to achieve high enough blood levels to attain 10 times the MIC of the infecting organisms (the concentration of antibiotic that is necessary for cure) in the CSF. Furthermore, as inflammation settles with therapy, the permeability of the blood-brain barrier decreases so that high blood levels are even more important.
3. Lumbar puncture—if you suspect bacterial meningitis, do not wait for an LP before giving antibiotics. The CSF will not be sterile by the time you do the LP (unless you are very slow).
4. A CT scan of the head does not have to be done immediately but it should be done since it provides evidence of focal disease. Never delay antibiotic therapy while awaiting a CT scan. The LP can be delayed if you feel there is likely to be a contraindication to it based on the CT results.

5. Search for a source for the meningitis. This includes a chest radiograph and a careful physical examination to rule out endocarditis; the CT scan will reveal a mastoid or sinus infection.
6. Supportive care—many patients will require initial management in an intensive care unit. Attention to their fluid and electrolyte balance is critical.
7. Patients who are alert may require analgesia for relief of headache.
8. Monitor carefully for both central nervous system (CNS) and systemic complications. The former include cerebral edema, hydrocephalus, brain abscess, subdural empyema or effusion, and cerebrovascular involvement (arterial and venous thrombosis). Systemic complications include septic shock, disseminated intravascular coagulation, adult respiratory distress syndrome, septic or reactive arthritis, and therapy-associated complications.

In most patients treatment of the meningitis results in total resolution of the headache within 7 to 10 days. Some patients suffer from lumbar puncture headache. This is more common in patients with aseptic meningitis in our experience but this most likely represents an ascertainment bias since the former group of patients are not nearly as ill as those with bacterial meningitis and hence are more likely to complain about ongoing headache.

Some patients have daily headaches following bacterial meningitis, which are usually associated with a normal neurologic examination. Patients who are headache free or who have only occasional headaches prior to the onset of meningitis are unlikely to have this pattern altered by the meningitis. In all likelihood the meningitis has served as a trigger to turn recurrent headaches into daily headaches. Since up to 17% of males and 20% of females have recurrent headaches it is surprising that more patients do not have daily headaches following meningitis.

Pathophysiology of Headache Due to Bacterial Meningitis

The pathogenesis of meningitis is as follows—bacteria colonize and penetrate the nasopharyngeal membrane and enter the blood stream. Invasion of the central nervous system then occurs. Bacteria multiply in the subarachnoid space leading to increased permeability of the blood-brain barrier. The bacteria and bacterial products induce transendothelial migration of granulocytes and monocytes with the release of cytokines and prostaglandins. The end result is cerebral edema, increased intracranial pressure, and impaired circulation.

It is evident from this overview of the pathogenesis of meningitis that headache in meningitis is due to vascular

dilatation mechanisms early in the illness, and that later in the course of the infection, it is as a result of increased intracranial pressure. [*Editors' note: Meningeal neurogenic inflammation probably adds to the head pain. Once the infection is effectively treated, some headache experts treat the pain with IV or IM DHE. The triptans may also be effective.*]

Selected Readings

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Editorial Comments

Bacterial meningitis is truly a life-threatening disorder, requiring early diagnosis, appropriate investigation, and effective management with parenteral antibiotics. Headache along with nuchal rigidity and fever are the major symptoms, but as the authors of this chapter point out the patients' descriptions of their headache symptoms may be poor for many reasons, especially because they are so sick. A high index of suspicion is needed in cases with bacterial meningitis which is treatable and curable. They say, somewhat tongue-in-cheek, that neurologists may have described the headache better. This is possible, but unlikely since most patients with bacterial meningitis are more often managed by non-neurologists!