



## **Headache and Inability to Solve Quadratic Equations**

Jonathan A. Edlow, MD

A 32-year old man presents to the ED complaining of 3 weeks of headache (HA) and difficulty with his work. He is a mathematics graduate student in a PhD program at MIT, and he is concerned because during the 3 week period that he has had the HA, he has noticed that his ability to solve quadratic equations, and perform simple differential calculus problems has become worse. Both the HA and the math difficulties began about 3 weeks ago, gradual onset and have increased gradually since then. The HA is 7/10 in severity, gradual in onset and has waxed and waned over the 3 weeks. He rarely gets HA's and this one is unfamiliar in quality, and feels "like a pressure" over his left fronto-parietal area without radiation. He has tried extra-strength Tylenol with "about 66.67% improvement."

He has noted nausea and vomited once the day before you see him. He denies neck pain or stiffness, fevers, chills, diplopia or changes in visual acuity, and weakness or numbness. The remainder of his ROS is negative, including no symptoms referable to the ears, sinuses, and respiratory, gastrointestinal or cardiovascular systems. There is no history of head trauma. His PHM is only noteworthy for mild asthma (never hospitalized, not on regular meds). He has no allergies. He does not smoke, and drinks socially (2-3 drinks per week). He is homosexual and has been in a monogamous relationship for 4 years. He tested negative for HIV a year ago. He is in the middle of defending his PhD thesis and has been having "philosophical differences of opinion" with his advisor.

On physical examination, he looks well. He is alert and oriented. His vital signs are T: 99.4 degrees, P: 72, BP: 128/72, and R: 14. His HEENT exam is completely normal and his neck is supple. The remainder of the general physical examination is normal, including absence of rash, lymphadenopathy and heart murmur. His neurological exam reveals a normal mental status, albeit the examiner was unable to test his mathematical abilities. Cranial nerves 2-12 were normal, including the presence of good venous pulsations. Motor was full without pronator drift. Sensation, cerebellar function, gait and reflexes were normal.

A diagnostic study was performed in the ED.

## **Key Clinical Questions**

What factors in the history and physical examination are used to determine which patients with non-traumatic HA should undergo further evaluation?

Is absence of fever useful in excluding brain abscess in patients with HA?

What is the pathophysiology of brain abscess?

What is the role of lumbar puncture in evaluating patients with possible brain abscess?

What clinical findings suggest a poor outcome in these patients?

## **Bacterial Brain Abscess**

### **Background, Risk Factors and Epidemiology**

Prior to the routine use of antibiotics for infections of the ears, sinuses, teeth and heart valves, bacterial brain abscess was a much more common disease than it is in 2003. Before 1900, brain abscess was almost always fatal, the diagnosis made at autopsy. In the late 1800s, the English surgeon William Macewan began treating these patients surgically, with has remained a mainstay of treatment to the present day. The nearly universal availability of CT scanning has revolutionized diagnosis of this condition and improvements in surgical techniques and the introduction of antibiotics has made an enormous impact on treatment. Currently the mortality rate has become markedly reduced.

### **Anatomy and Pathophysiology**

Brain abscess is a focal, intracerebral infection that can be due to bacteria, fungi and protozoa. The blood-brain barrier (BBB) is relatively resistant to penetration of these microorganisms from the blood into the brain, which accounts for the relative rarity of this condition, despite the frequency of bacteremia. In fact, researchers must directly inoculate experimental animals to produce brain abscess because production of an abscess from intravenous placement of bacteria usually does not lead to abscess formation. In patients, the abscess will occasionally form in an abnormal area of brain (infarction, tumor or hematoma); however most develop in areas of previously normal brain tissue.

Bacteria can gain access to the CNS from direct extension of a contiguous infection (e.g., sinusitis), from transit through the valveless emissary veins into the intra-cranial venous system, from direct penetration (e.g., post-surgical or penetrating trauma), from bacteremia (see above). In 20-30% of cases of brain abscess, none of these mechanisms is identified, leading to the so-called "cryptogenic abscess".

Once the microorganism has penetrated the BBB, there is a well-defined evolution of pathological changes, as listed below:

- Early cerebritis: days 1-3 (focal inflammation and edema)
- Late cerebritis: days 4-9 (development of a necrotic center)
- Early capsule: days 10-14 (establishment of a ring-enhancing vascularized capsule)
- Late capsule: beyond day 14 (further development of a walled off capsule)

The location can be anywhere in the head, and is often a clue as to the pathogenesis. For example, when the focus is the paranasal sinuses, frontal lobe abscesses are more common. Otogenic infections usually create temporal lobe and cerebellar abscesses. When bacteremia is the source, the infection can develop anywhere, but most commonly in the middle cerebral artery territory and often with multiple abscesses. When the cause is due to penetrating trauma or post-neurosurgery, the location is related variable. As well, the microbial flora tend to portend the source (see chart below).

<b>Source</b>	<b>Location</b>	<b>Microbes</b>	<b>Treatment</b>
Paranasal sinuses	Frontal lobe	Aerobic & anaerobic streptococci Hemophilus sp. Anaerobes (bacteroides, fusobacteria)	Penicillin (or cefotaxime) + Metronidazole
Otogenic	Temporal lobe Cerebellum	Streptococci Enterobacteriaceae Pseudomonas aeruginosa Bacteroides sp.	Penicillin + Metronidazole + Ceftazidime
Hematogenous	Multiple lesions, often in the MCA territory	Depends on source <ul style="list-style-type: none"> <li>• Endocarditis</li> <li>• Urinary tract</li> <li>• Intra-abdominal</li> <li>• Lung abscess</li> </ul>	Nafcillin + Metronidazole + Cefotaxime
Penetrating trauma	Depends on site	Staph aureus Clostridia sp. Enterobacteriaceae	Nafcillin + Cefotaxime
Postoperative	Variable	Staph epi, and aureus Enterobacteriaceae Pseudomonal sp.	Vancomycin + Ceftazidime

(Chart adapted from reference 1)

## **ED Presentation**

Most patients who are able to give a cogent history complain of HA. There is nothing in the details of the HA that distinguish one from a brain abscess from the myriad of other causes of HA. Abrupt onset suggests another diagnosis. Sometimes, abrupt worsening will occur with rupture of a brain abscess into a ventricle, but this complication is usually fatal and is associated with a severely ill patient. Seizures may occur, as well as symptoms of raised ICP (drowsiness, nausea and vomiting, lethargy and stupor).

Fever is by no means universal being present in less than 50% of cases. In one series, while 50% had a history of fever, only 25% had documented fever on presentation. Focal neurological signs (hemi-motor or sensory symptoms, ataxia and aphasia) occur in 35-50% of cases and will depend entirely on where the abscess is located. Cerebellar abscesses are usually associated with ataxia and dizziness. Brainstem abscesses are usually associated with cranial nerve findings. Note that in patients with frontal lobe masses, even relatively large ones, the physical exam is often quite insensitive. These patients frequently will complain of “soft”, odd sorts of symptoms that they are aware of, but that are difficult if not impossible to test.

Papilledema is found in 25% of patients with brain abscess. Findings suggestive of a source from HEENT infection, endocarditis or other bacteremia may be found in variable amounts of patients. Unfortunately, in the absence of focal neurological findings or changes in mental status, there is little to specifically suggest the diagnosis, which accounts for the frequency with which the diagnosis is initially missed.

## **Lab Studies**

Standard laboratory testing is rarely helpful. The WBC count is often normal, and the ESR, while usually elevated, can be normal, and is not a standard ED test for patients with HA unless temporal arteritis is suspected. Blood cultures, while usually negative, should be obtained. Performing a lumbar puncture is not recommended if brain abscess is being considered. This is one condition in which transtentorial herniation has been reported, and more importantly, the CSF analysis is rarely diagnostically useful. The findings range from normal, for deep-seated abscesses, to non-specifically abnormal (elevated protein and pleocytosis) in most, to diagnostic in the extraordinary patient with either ventricular rupture or ventriculitis from adjacent pus. In these latter patients, LP would likely be clinically contraindicated.

At surgery, or at stereotactic brain biopsy, pus is cultured. This is vitally important since the course of therapy often lasts for 6-8 weeks and is parenteral. This is obviously not done in the ED, but with modern microbiological techniques, the organism is almost always isolated.

## **Imaging Studies**

CT and MR have completely revolutionized the diagnosis of brain abscess. The four pathological stages can be seen radiographically. The earliest stages of cerebritis will usually show some vasogenic edema (black on non-contrast CT). It is worth mentioning brain abscess to the radiologist, since contrast will often be administered. As well, sometimes repeat images taken 30-60 minutes after contrast injection, will sometimes clarify an early cerebritis. By MR, T-1 imaging, edema appears hypo-intense (black), while on T-2 imaging, the edema appears white. Later on in the patient's course, repeated imaging is used to follow the response to therapy.

It is also important to recall that a ring-enhancing lesion by CT has a differential diagnosis that includes tumor (both primary brain, metastatic and lymphoma), necrotizing encephalitis, infarction, granuloma, as well as abscess due to toxoplasmosis and fungi. If brain abscess is high in the differential diagnosis, MR is preferable to CT when it is available.

More advanced imaging studies are sometimes performed but are rarely if ever necessary in the ED.

## **Procedures**

As mentioned above, LP is potentially dangerous and notoriously non-helpful in diagnosing brain abscess. However if meningitis is a serious consideration, and the patient has no focal neurological abnormalities and a normal mental status, especially if venous pulsations are present, then emergent LP would be the correct procedure to exclude meningitis. However if the situation is unclear, or if there are neurological abnormalities, then the patient should be first treated with parenteral antibiotics, then scanned, and then tapped if safe based on the imaging results.

## **Emergency Department Care**

Establishing the correct diagnosis is the major priority for any ED patient with HA, since rational therapy will more likely follow correct diagnosis. If meningitis is a real possibility, parenteral antibiotics should be given as rapidly as possible. Similarly, in the sick patient with brain abscess (focal or generalized neurological findings), rapid empiric antibiotics should also be given. However in stable patients without the above findings, and after discussion with the admitted neurosurgeon, it is reasonable to withhold antimicrobials. This is because parenteral antibiotics may decrease the ability to get a proper culture, and it is this result that will guide as many as 2 months of parenteral antibiotics. This decision must be individualized. When antibiotics are administered in the ED, they are empiric and targeted at the likely pathogens. As with abscesses in many parts of the body, antimicrobial therapy is usually an adjunct to drainage.

The dosages of the antibiotics for most patients are as follows (all are given IV):

- Penicillin G: 2-4 million units q4h
- Metronidazole: 500 mg q6h
- Cefotaxime: 1-2 gm q4-8h (max 12 gm/d)
- Ceftazidime: 1-2 gm q4-8h (max 12 gm/d)
- Nafcillin: 2 gm q4h
- Vancomycin: 1 gm q12h

## **Consultations and Admission**

The ED physician should admit all patients with brain abscess, barring extenuating circumstances and assuming that neurosurgical expertise is available at the hospital. If not, the patient should be transferred to a center with such expertise. As well, in some cases, even when there is neurosurgical expertise, transfer is reasonable if it is to a center with stereotactic biopsy capability. These patients are almost always admitted to the neurosurgery or neurology service. Antibiotics and needle drainage may cure some patients, who are treated in the cerebritis or early cavity phase. The needle drainage can be accomplished using stereotactic technique.

## **Summary**

Brain abscess is a relatively uncommon, and difficult to diagnose entity that causes HA in the ED. That said, once suspected, modern imaging has made that diagnosis far easier to establish. It is important to remember that normal physical exam, absence of fever and a normal WBC count do not exclude brain abscess. Once established, the ED physician must consult neurosurgery, discuss empiric antibiotics and decide about transferring the patient to a center with the required expertise. If meningitis is a serious concern, antibiotics should be rapidly administered.

## **Key learning points**

1. Patients whose HA onset is abrupt in onset, new for them, or qualitatively different from prior HA, severe, or have associated symptoms or signs suggesting elevated intracranial pressure or mass, should be considered for further evaluation beyond history and physical examination. This is especially true if there is no alternative (benign) diagnosis that is likely.
2. Many patients with brain abscess do not have fever and many will not have an elevated WBC count.
3. Patients with frontal lobe processes of any kind (tumor, hematoma, abscess) are often clinically silent. The symptoms that do occur are often vague and subtle – “soft” symptoms.

4. The likely organisms causing and location of bacterial brain abscess varies with the pathophysiology of the abscess. History and physical examination should target likely causes – the ears, paranasal sinuses and sources of bacteremia.
5. Bacterial brain abscess is a neurosurgical disease although there are cases in which stereotactic needle aspiration and IV antibiotics are curative.

## **References**

1. Brain abscess; Mathisen GE and Johnson JP; *Clinical Infectious Diseases*; 25: 763-81; 1997.
2. Bacterial brain abscesses: factors influencing mortality and sequelae; Seydoux Ch and Francioli P; *Clinical Infectious Diseases*; 15: 394-401; 1992.
3. The clinical presentation of intracranial abscesses; Harrison MJG; *Quarterly Journal of Medicine*; New series LI (#204): 461-468; 1082.
4. CNS complications of ENT infections: an analysis of 50 consecutive cases; Kraus M and Tovi F; *Journal of Otolaryngology*; 20: 329-335; 1991.
5. Bacterial brain abscess: microbiological features, epidemiological trends and therapeutic outcomes; Lu CH, Chang WN, Lin YC et al; *Quarterly Journal of Medicine*; 95: 501-509; 2002.
6. Outcome of medical treatment of bacterial abscesses without therapeutic drainage: review of cases reported in the literature; Bamberger DM; *Clinical Infectious Diseases*; 23: 592-603; 1996.
7. CNS infections in the compromised host: a diagnostic approach; Cunha BA; *Infectious disease clinics of North America*; 15: 567-590; 2001.

## **Bacterial brain abscess**

### **Outcome of Case**

The diagnostic procedure was a cranial CT scan, both with and without contrast. The non-contrast scan showed a large area of hypodense vasogenic edema in the left frontal lobe. There was ring-enhancement on the enhanced scan. Brain abscess was diagnosed. This patient was transferred to a facility that had both neurosurgical expertise as well as the ability to perform stereotactic biopsy. This latter procedure was performed on the first hospital day. The blood cultures drawn in the ED were negative but the pus that was obtained at biopsy grew out mixed flora, including aerobic and anaerobic streptococci. HIV antibody testing was negative.

The patient was treated for 6 weeks with high dose parenteral penicillin G and metronidazole. He never required an open surgical procedure and follow-up CT scans showed gradual resolution of the abscess. His HA disappeared rapidly and his ability to solve complex mathematical problems improved to his baseline. This inability to do higher math was his only physical finding, not unusual for patients with frontal lobe pathology. An extensive evaluation of his heart, ears, teeth and sinuses never revealed the source for the abscess, making this patient among the 20-30% who are termed “cryptogenic” in terms of etiology.

## **Annotated Bibliography**

- 1. Brain abscess;** Mathisen GE and Johnson JP; *Clinical Infectious Diseases*; 25: 763-81; 1997

This is an excellent and fairly recent thorough review of the subject. It includes a good discussion of the pathophysiology, bacteriology, diagnostic evaluation and treatment of brain abscess. It is also very well documented.

- 2. Bacterial brain abscesses: factors influencing mortality and sequelae;** Seydoux Ch and Francioli P; *Clinical Infectious Diseases*; 15: 394-401; 1992

This article reviews 39 cases in the CT era, with an analysis of factors that affect outcome. Not surprisingly, sicker patients, as identified with 2 factors: rapid progression of symptoms and poor mental status on admission predicted poor clinical outcomes.

- 3. The clinical presentation of intracranial abscesses;** Harrison MJG; *Quarterly Journal of Medicine*; New series LI (#204): 461-468; 1982.

An older paper this still provides an excellent account of clinical symptoms and signs. Headache was the most common symptom, found in 80% of patients. While 50% complained of fever as a symptom, only 25% had documented fever on presentation. Nearly 30% of patients had frontal lobe abscesses and another 30% had temporal lobe locations. As well, about 50% of patients had histories of more than 2 weeks duration.

- 4. CNS complications of ENT infections: an analysis of 50 consecutive cases;** Kraus M and Tovi F; *Journal of Otolaryngology*; 20: 329-335; 1991.

A useful review from a single institution, this article describes not only brain abscess, but also the other intracranial complications of ENT infections, which include meningitis, cerebral venous sinus thrombosis, subdural and epidural empyema (abscess). Frontal bone osteomyelitis (also known as Pott's puffy tumor) is another "extracranial" complication of frontal sinusitis.

- 5. Bacterial brain abscess: microbiological features, epidemiological trends and therapeutic outcomes;** Lu CH, Chang WN, Lin YC et al; *Quarterly Journal of Medicine*; 95: 501-509; 2002. ()

This recent retrospective review examines 123 cases over a 15-year period. The investigators compared the first half of the time period with the latter half and found that Gram-negative organisms were more common in the latter period.

- 6. Outcome of medical treatment of bacterial abscesses without therapeutic drainage: review of cases reported in the literature;** Bamberger DM; Clinical Infectious Diseases; 23: 592-603; 1996.

These patients are mostly ones with non-brain abscesses; however some are CNS lesions. Factors associated with poor response to medical treatment were size (> 5cm, polymicrobial infection, presence of Gram-negative bacilli, length of treatment of < 4 weeks and use of an aminoglycoside as the only agent.

- 7. CNS infections in the compromised host: a diagnostic approach;** Cunha BA; Infectious disease clinics of North America; 15: 567-590; 2001.

This is a nice review of CNS infections in compromised hosts. The author points out that these infections tend to be more subacute and indolent, with more pathogens (and different ones compared with immunocompetent hosts. Brain abscess was more common in the compromised hosts.

## **Questions**

1. The pathophysiology of bacterial brain abscess includes all but which of the following:
  - a. Contiguous spread from an ear or mastoid infection
  - b. Contiguous spread from sinusitis
  - c. Introduction of organisms from surgery or trauma
  - d. Introduction of organisms by mosquito-borne vector
  - e. Hematogenous spread
  
2. The most common symptom in awake patients with brain abscess is:
  - a. Seizure
  - b. Headache
  - c. Double vision
  - d. Stiff neck
  - e. Vomiting
  
3. Fever is present in most patients with brain abscess
  - a. True
  - b. False
  
4. In brain abscess, an LP would be expected to routinely show all of the following except:
  - a. Normal protein and opening pressure
  - b. Greater than 1,000 WBC per mm<sup>3</sup>
  - c. Culture positive for the causative organism
  - d. None of the above
  
5. Treatment for brain abscess includes antibiotics and always requires open surgical drainage.
  - a. True
  - b. False
  
6. The causative organisms in brain abscess are at least partly a function of the pathophysiology.
  - a. True
  - b. False

**Answers**

1. **D is the correct answer.** All of the others are clear-cut mechanisms for development of a brain abscess. While mosquito-borne viruses can cause encephalitis (West Nile, Eastern Equine, and others), this is not a known cause of bacterial brain abscess.
2. **B is the correct answer.** While all of the listed symptoms could be associated with brain abscess, headache is clearly the most common. Except in lethargic patients, most conscious patients with brain abscess have headache. Seizure is next and occurs in ~ 50% of cases.
3. **B is correct; the statement is false.** In fact fever only occurs in approximately 50% of brain abscesses, even in normal hosts. The absence of fever should in no way dissuade one from considering the diagnosis.
4. **D is correct; none of the above.** LP is simply not a very useful test for brain abscess. As well, there is some risk of herniation, albeit small. The main reason that LP is not useful is that the findings are non-specific (elevated protein and opening pressure). Cell counts can be low (or normal), and culture is usually negative and so does not guide therapy.
5. **B is correct; the statement is false.** This is one reason that patients should be considered for transfer to a center that can accomplish stereotactic drainage. Some patients will be cured with percutaneous drainage and IV antibiotics, and not require open surgical drainage.
6. **A is correct; the statement is true.** Abscesses from contiguous spread tend to be organisms that cause ENT infections. Abscesses from hematogenous sources will depend on the source. Post-traumatic are more commonly Staph while post-operative abscesses can be Staph epi. This helps guide the initial antibiotic selections.