Chapter 119

# Headache Attributed to Infection

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## HEADACHE ATTRIBUTED TO INTRACRANIAL INFECTION

Headache attributed to intracranial infection is a new headache in close temporal relation with an intracranial infection that is resolved after the remission of the infection.

**Other Terms:** Central nervous system (CNS) infection headache or headache caused by CNS infection are discouraged.

## International Headache Society (IHS) Codes, IHS Diagnostic Criteria (16), and Clinical Presentation

9.1 Headache attributed to intracranial infection (WHO ICD-10NA code 44.821)

9.1.1 Headache attributed to bacterial meningitis

Diagnostic criteria:

**A.** Headache with at least one of the following characteristics and fulfilling criteria C and D:
  **1.** Diffuse pain
  **2.** Intensity increasing to severe
  **3.** Associated with nausea, photophobia, and/or phonophobia
**B.** Evidence of bacterial meningitis from examination of cerebrospinal fluid (CSF).
**C.** Headache develops during the meningitis.
**D.** One or other of the following:
  **1.** Headache resolves within 3 months after relief from meningitis.
  **2.** Headache persists but 3 months have not yet passed since relief from meningitis.

9.1.2 Headache attributed to lymphocytic meningitis

Diagnostic criteria:

**A.** Headache with at least one of the following characteristics and fulfilling criteria C and D:
  **1.** Acute onset
  **2.** Severe intensity
  **3.** Associated with nuchal rigidity, fever, nausea, photophobia, and/or phonophobia
**B.** Examination of CSF shows lymphocytic pleocytosis, mildly elevated protein, and normal glucose.
**C.** Headache develops in close temporal association to meningitis.
**D.** Headache resolves within 3 months after successful treatment or spontaneous remission of infection.

9.1.3 Headache attributed to encephalitis

Diagnostic criteria:

**A.** Headache with at least one of the following characteristics and fulfilling criteria C and D:
  **1.** Diffuse pain
  **2.** Intensity increasing to severe
  **3.** Associated with nausea, photophobia, or phonophobia
**B.** Neurologic symptoms and signs of acute encephalitis, and diagnosis confirmed by electroencephalogram (EEG), CSF examination, neuroimaging, and/or other laboratory investigations.
**C.** Headache develops during encephalitis.
**D.** Headache resolves within 3 months after successful treatment or spontaneous remission of the infection.

9.1.4 Headache attributed to brain abscess

Diagnostic criteria:

**A.** Headache with at least one of the following characteristics and fulfilling criteria C and D:
  **1.** Bilateral
  **2.** Constant pain
  **3.** Intensity gradually increasing to moderate or severe
  **4.** Aggravated by straining
  **5.** Accompanied by nausea
**B.** Neuroimaging and/or laboratory evidence of brain abscess.

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**C.** Headache develops during active infection.
**D.** Headache resolves within 3 months after successful treatment of the abscess.

9.1.5 Headache attributed to subdural empyema

Diagnostic criteria:

**A.** Headache with at least one of the following characteristics and fulfilling criteria C and D:
  **1.** Unilateral or much more intense on one side
  **2.** Associated with tenderness of the skull
  **3.** Accompanied by fever
  **4.** Accompanied by stiffness of the neck
**B.** Neuroimaging and/or laboratory evidence of subdural empyema.
**C.** Headache develops during active infection and is localized to or maximal at the site of the empyema.
**D.** Headache resolves within 3 months after successful treatment of the empyema.

A secondary headache is attributed to intracranial infection when a new headache occurs in close temporal relation to a proven intracranial infection. The headache disappears after successful treatment or spontaneous remission of the infection.

Such a new diffuse and often pulsating headache combined with neck stiffness, fever, photophobia, malaise, vomiting, altered consciousness, and confusion represents one of the clinical hallmarks of intracranial infections. These symptoms, clinically summarized as "meningeal syndrome," are extremely important and constitute a serious warning sign. Intracranial infections such as bacterial meningitis, encephalitis, and brain abscesses are medical emergencies that need immediate diagnosis, antimicrobial treatment, and quite often supportive intensive care. The clinical symptoms of bacterial meningitis and certain viral diseases, including headache, progress rapidly, whereas symptoms of a brain abscess or subdural empyema may develop over a more protracted time frame. Also, headaches of subdural empyema or brain abscesses are more likely lateralized. Finally, headaches of CNS infections may exhibit characteristics of primary headaches such as migraine tension-type or cluster headache. A number of case reports indicate that various primary headache-like presentations can be encountered with intracranial infection, such as tension-type headache in patients with subacute Borrelia meningitis (8). The character and type of headache is not believed to be helpful to distinguish between underlying infectious causes, but reliable clinical data are missing.

To prove the intracranial origin or manifestation of an infection, a CSF examination is necessary. In cases of unclear fever and headache, a CSF examination is highly recommended to exclude or prove the diagnosis of CNS infection.

The diagnosis of acute CNS infections is established by:

**1.** Elevation of the CSF cell count and other parameters (see Table 119-1)
**2.** Identification of the causative microorganism by culture, Gram-stain, or polymerase chain reaction (PCR).

A computed tomography (CT) of the head is necessary prior to the lumbar puncture in the cases with focal neurologic signs and/or a disturbance of consciousness (15). To diagnose brain abscess or subdural empyema, a CT or magnetic resonance imaging (MRI) scan of the head with contrast medium is essential. Herpes simplex encephalitis, one of the most serious and acute diseases, can be diagnosed by PCR technique with a sensitivity and specificity over 90% in the first week of encephalitis (19). Other

**TABLE 119-1 Typical Findings in the Cerebrospinal Fluid**

| | >90% polymorphonuclear leukocytes (purulent meningitis) | Mixed pleocytosis with polymorphonuclear leukocytes and lymphocytes | >80% lymphocytes (viral meningoencephalitis) |
|---|---|---|---|
| Etiology | *Streptococcus pneumoniae,* *Neisseria meningitidis,* streptococci (group B), *Escherichia coli,* *Haemophilus influenzae* | Ineffectively treated bacterial meningitis<br>*Mycobacterium tuberculosis*<br>*Listeria monocytogenes*<br>*Toxoplasma gondii*<br>*Candida albicans*<br>*Cysticercus cellulosa*<br>*Borrelia burgdorferi*<br>Abscess, empyema<br>Leptomeningeal metastasis | Adenovirus, arbovirus, herpes virus, myxovirus, enterovirus, smallpox, rubella, rhabdovirus, JC virus, and HIV<br>*Cryptococcus neoformans*<br>*Borrelia burgdorferi* |
| Cell count | >800/$\mu$l | <500/$\mu$l | <800/$\mu$l |
| Protein | <1000, 50 % >2000 mg/L | <1000–10,000 mg/L | <1000 mg/L |
| Glucose (CSF/serum quotient) | <0.4 | <0.4 tuberculosis and leptomeningeal metastasis | 0.5–0.6 |
| Lactate | >3.8 mmol/L | >3.8 mmol/L tuberculosis | Normal |

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viral diseases are harder to verify because viral cultures are unreliable, PCR sensitivity is poor, and titer changes are detected with a delay (18).

It is extremely important to recognize that the absence of headache does not exclude CNS infections. Children, elderly and immunocompromised patients, and patients with diabetes mellitus or alcohol abuse do not necessarily develop meningeal syndrome and report no or just minimal headache.

CNS infection headache usually resolves with successful antimicrobial treatment or the spontaneous remission of the disease within 1, or at most 3, months.

## Epidemiology

Headache is one of the major symptoms of the meningeal syndrome. In up to 92% of patients with proven bacterial meningitis, meningism and headache is reported (1), but the problem is more complex with viral meningoencephalitis. Headache is a major complaint in such patients with viral illness but reliable data on its incidence, and the effect of a particular agent on such incidence, are missing. Enteroviral meningitis, for example, is accompanied by severe headache in up to 90% (27). Finally, patients with brain abscess report headache as a major symptom in 65 to 90% of cases (30).

In a recent study on sudden-onset headache, only 4 out of 135 patients had lymphocytic meningitis and none had bacterial meningitis (20). This may indicate that in acute diseases such as bacterial meningitis, headache is covered by other symptoms or summarized as a part of meningeal irritation. This hypothesis needs further testing in large observational studies.

## Pathophysiology

Headache and meningism are clinical manifestations of meningeal irritation (Fig. 119-1). Bacteria as well as viruses may directly activate meningeal nerve fibers and cause neuropeptide release. Neuropeptides are significantly raised in the CSF of patients with proven bacterial meningitis (17). Active bacterial metabolism engenders toxic products, such as $H_2O_2$ and pore-forming toxins. In addition, bacterial cell wall and surface structures, such as peptidoglycan, lipoteichoic acids, and lipopolysaccharide, may directly activate sensory nerve fibers in the meninges. These components induce several inflammatory mediators in different relevant cell types including endothelial cells and microglia (28). Cytokines and nitric oxide (NO) are mediators known to play a role in headache (26).

CNS infections are characterized by a significant influx of activated leukocytes, which in turn may add to the activation of meningeal nerve fibers (Fig. 119-2). Increased blood flow and cytotoxic effects contribute to brain edema, which may cause tension on the meninges. As in other

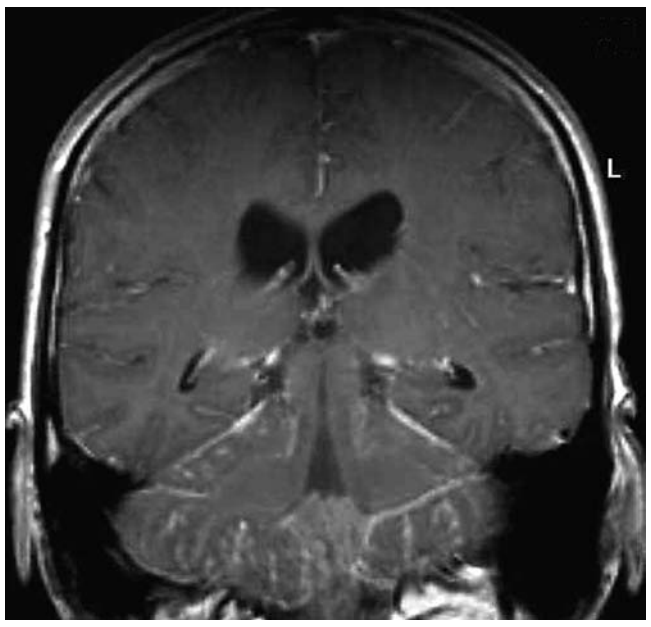


***FIGURE 119-1.*** Magnetic resonance imaging (MRI) scan of a patient with proven tuberculous meningitis and history of a newly developed headache several days before admission. The T1 sequence with contrast medium shows meningeal enhancement as a sign of meningeal inflammation. (MRI is courtesy of Dr. R. Klingebiel, Charité, Berlin.)

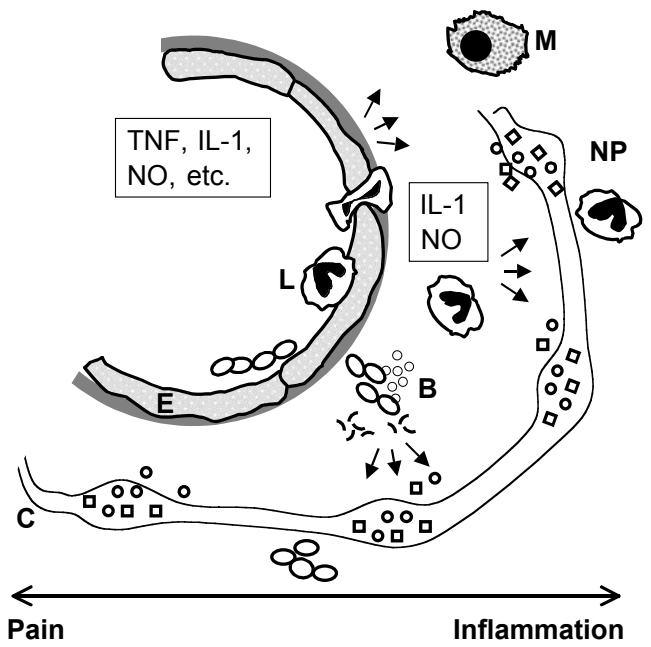


***FIGURE 119-2.*** Hypothetical concept of the interactions between microbial, host response–driven inflammation and neurogenic mechanism. C, C-fibers; M, macrophages; B, bacteria, bacterial components, and toxins; L, leukocytes; NP, neuropeptides.

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conditions, edema and space-occupying lesions in encephalitis, brain abscess, and empyema can cause headache.

## Treatment and Management

The management of headache associated with intracranial infection includes infection-specific treatment, supportive care, and analgesics. Bacterial meningitis requires immediate antibiotic therapy. Treatment with high-dose amoxicillin is sufficient in community-acquired bacterial meningitis in western Europe but is inadequate in most parts of the United States or southern Europe (10). The choice of antibiotics, therefore, depends on the local bacterial resistance patterns, and consultation with infectious disease and microbiology experts is strongly recommended.

Dexamethasone has been shown to reduce mortality and neurologic sequelae significantly, but its effect on acute headache or chronic postinfection headache remains unclear (10). Herpes simplex encephalitis requires immediate treatment with acyclovir (10 mg/kg body weight every 8 hours).

Simple nonsteroidal anti-inflammatory drugs (NSAIDs) such as paracetamol often are sufficient to control headache attributed to CNS infection. Usually, it resolves quickly with effective antimicrobial treatment. Specific migraine or cluster headache treatments such as ergots or triptans generally are not recommended. Their vasoconstrictive potential may complicate vasospasm, a known complication in bacterial or herpes zoster meningitis. In general, the existence of brain edema requires high perfusion pressure. Consequently, substances potentially reducing cerebral blood flow should be avoided.

# HEADACHE ATTRIBUTED TO SYSTEMIC INFECTION

Headache attributed to systemic infection is a new symptom or a new type that occurs concomitantly with a systemic infection and disappears after less than 1 month of remission of the infection.

**Other terms:** Fever-related headache, headache caused by microorganisms, toxemic headache, septicemic headache, headache as part of the infectious disease syndrome

## IHS Codes, IHS Diagnostic Criteria (16), and Clinical Presentation

9.2 Headache attributed to systemic infection [WHO ICD-10NA code 44.881]

Diagnostic criteria:

**A.** Headache with at least one of the following characteristics and fulfilling criteria C and D:
  **1.** Diffuse pain
  **2.** Intensity increasing to moderate or severe
  **3.** Associated with fever, general malaise, or other symptoms of systemic infection

**B.** Evidence of systemic infection.

**C.** Headache develops during the systemic infection.

**D.** Headache resolves within 72 hours after effective treatment of the infection.

9.2.1 Headache attributed to systemic bacterial infection

Diagnostic criteria:

**A.** Headache fulfilling criteria for 9.2 Headache attributed to systemic infection.

**B.** Laboratory investigation discloses the inflammatory reaction and identifies the organism.

9.2.1 Headache attributed to systemic viral infection

Diagnostic criteria:

**A.** Headache fulfilling criteria for 9.2 Headache attributed to systemic infection

**B.** Clinical and laboratory (serology and/or PCR molecular) diagnosis of viral infection

9.2.2 Headache attributed to other systemic infection

Diagnostic criteria:

**A.** Headache fulfilling criteria for 9.2 Headache attributed to systemic infection

**B.** Clinical and laboratory (serology, microscopy, culture, or PCR molecular) diagnosis of infection other than bacterial or viral

Headaches secondary to systemic infections generally are nonspecific features and described as diffuse and moderate to severe. They are most often associated with fever, general malaise, and clinical symptoms of, or laboratory evidence for, systemic infection (11). Although headache is commonly reported in the medical history of patients suffering from infectious diseases, surprisingly little is known about other clinical features of the headache and its relationship to complaints such as myalgia and malaise. Headache does not necessarily depend on the existence of fever.

Migraine, tension-type (9), and cluster headache (4) may be induced or worsened by nonencephalitic infections in patients who have an established history of these disorders. The association of specific viruses like herpes simplex with cluster headache has been proposed, but a causative relationship remains uncertain (14). Approximately 25% of patients with viral influenza complain of retro-orbital headache (23).

It is important to differentiate between just headache as a symptom of a general infection and one that heralds a primary or secondary CNS infection. Therefore, CSF examination is essential in all suspicious cases, particularly in the presence of neurologic symptoms such as meningism, focal neurologic signs, seizures, and disturbance of consciousness. If there is doubt it is recommended to exclude

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an intracranial manifestation of an infection by CSF examination, particularly in severely ill patients.

## Epidemiology

Little is known of the nature and exact prevalence of headache attributed to systemic infections. It often accompanies common infections such as influenza and rare ones such as malaria, brucellosis, and leptospirosis (2), but the epidemiology of these infections varies widely, depending on the season, geographic location, and individual patterns of disease.

Headache may accompany sepsis as part of septic encephalopathy (12). Volunteers injected intravenously with lipopolysaccharide, a major inflammatory component of Gram-negative bacteria, 83% developed a sterile inflammatory response and 83% complained of, serving as a model for sepsis, and develop severe headache; the rest reported mild headache (21). Viral influenza infections are accompanied by headache in 60 to 100% of the cases, particularly in the presence of fever (23). Other viral infections such as adenovirus, Oropouche virus, Venezuelan equine encephalitis, West Nile virus, and dengue are associated with severe headache in up to 80% of the cases (2,8). Some studies also report nausea, photophobia, and vomiting, but do not provide good evidence to rule out meningeal infection by CSF exams.

Systemic infections such as *Rickettsia*, *Ehrlichia canis*, *Borrelia burgdorferi*, and Q fever are commonly associated with headache in up to 90% of cases (24,25). Malaria and brucellosis may cause headache in up to 40% of patients. Finally, *Legionella pneumophila* and *Mycoplasma* pneumonia as well as leptospirosis are accompanied by headache. Most of the mentioned pathogens may directly involve intracranial structures such as the meninges or cause secondary CNS vasculitis.

## Pathophysiology

The exact nature of pain mechanisms in headache associated with systemic infections remains unclear. Although fever may play an important role, headache is not simply only mediated through fever. Lipopolysaccharide (LPS) induces headache in healthy volunteers and blocking LPS recognition with a lipid A analog inhibits the headache (21). The mechanisms of this effect most likely are mediated through the interleukin (IL) cascade. It is likely that several other surface components and metabolic products of bacteria cause headache by a similar effect since, in experimental models, induction of IL-1 caused a cascade of mediators (e.g., NO, prostaglandins, other cytokines) that may play a significant role in headache generation (26) (Fig. 119-2). The mechanisms of headache attributed to viral infections such as influenza remain elusive.

## Treatment and Management

When headache is a caused by an underlying infection, a specific treatment directed to the bacteria or virus is essential. Additionally, antipyretic and NSAIDs are recommended. Patients who are predisposed to primary headache disorders and who develop systemic infection-induced migraine or cluster or tension-type headache should receive headache-specific therapy. It should be noted that ergotamine and drugs interacting with serotonin should not be given with erythromycin.

# HEADACHE ATTRIBUTED TO HIV/AIDS

Headache attributed to HIV/AIDS is a headache resulting from HIV infection or intracranial opportunistic infections.

## IHS Codes, IHS Diagnostic Criteria (16), and Clinical Presentation

9.3 Headache attributed to HIV/AIDS [WHO ICD-10NA code 44.821]

Diagnostic criteria:

**A.** Headache with variable mode of onset, site, and intensity[1] fulfilling criteria C and D.
**B.** Confirmation of HIV infection and/or of the diagnosis of AIDS, and of the presence of HIV/AIDS-related pathophysiology likely to cause headache, by neuroimaging, CSF examination, EEG, and laboratory investigations.
**C.** Headache develops in close temporal relation to the HIV/AIDS-related pathophysiology.
**D.** Headache resolves within 3 months after the infection subsides.

*Coded elsewhere:* Headache attributed to a specific supervening infection is coded according to that infection.

Headache is a prominent symptom in HIV infection (6). Generally, it is dull and bilateral, reminiscent of tension-type headache (6). The confirmation of HIV infection is essential to discriminate headache caused by additional intracranial conditions that are associated with HIV infections (e.g., cryptococcal meningitis). Therefore, it is crucial to obtain neuroimaging studies and CSF examination to distinguish between headache as a general sympton of systemic HIV infection and one that is caused by CNS infections or conditions that accompany HIV disease. Headache in AIDS can also be caused by secondary CNS infections as well as by tumors. Common infections in HIV or AIDS patients are toxoplasmosis, cryptococcal disease, tuberculosis, and cytomegalovirus (18,29). Primary CNS lymphoma and metastatic systemic lymphoma are the most common in HIV patients (22). Headache associated with intracranial infections or tumors has the features associated

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with the underlying causes. HIV infection may trigger primary headaches in predisposed patients, and it seems that the immunologic state of the patients influences the manifestation and frequency of these headaches. Interestingly, advanced stages of AIDS correlate with a decrease of migraine frequency and intensity (13).

### Epidemiology

The prevalence of headache in HIV infection varies between 10 and 55% (6). This wide range can be explained by differences in study design and definitions of headache, which in most reports did not conform to the IHS criteria.

### Pathophysiology

The pathophysiology of HIV-related headache remains speculative. HIV virus may cause aseptic meningitis and activation of microglia and astroglia (22), which in turn may activate trigeminal nerve fibers. The underlying molecular events are unclear. Secondary opportunistic infection may cause headache through either space-occupying effects or inflammatory mediators.

### Treatment and Management

There is no specific treatment for headache attributed to HIV infection. How highly active antiretroviral therapy (HAART) affects headache is not well studied. Headache as a side effect of HAART should also be considered.

Symptomatic treatment with analgesics or NSAIDs is recommended. Primary headaches should be treated according to recommendations for the specific headache types. In cases of a proven opportunistic CNS infection, a specific antimicrobial treatment should be initiated.

## CHRONIC POSTINFECTION HEADACHE

Chronic postinfection headache persists longer than 3 months after the resolution of an intracranial infection.

### IHS Code, IHS Diagnostic Criteria (16), and Clinical Presentation

9.3 Chronic postinfection headache [WHO ICD-10NA code 44.821 or 44.881; code to specific etiology]

Diagnostic criteria:

**A.** Headache with at least one of the following characteristics and fulfilling criteria C and D:
  **1.** Diffuse continuous pain
  **2.** Associated with dizziness
  **3.** Associated with difficulty in concentrating and/or loss of memory

**B.** Evidence of previous intracranial bacterial infection from CSF examination or neuroimaging.
**C.** Headache is a direct continuation of 9.1.1 Headache attributed to bacterial meningitis.
**D.** Headache persists for >3 months after resolution of infection.

Up to 30% of survivors of bacterial meningitis report diffuse and continuous headache (4,6). The headache may be associated with dizziness or neuropsychologic disturbances such as concentration deficits or memory loss. Some case reports and one study report chronic postinfection headache (4,6). There is no convincing evidence for persistent headache following other infections. Prospective studies are necessary to further characterize postinfection headache. Also, these studies may clarify the influence of intracranial infection on underlying primary headaches.

A diagnosis of chronic postinfection headache should only be made with proven history of bacterial meningitis in the history and after careful exclusion of other headache causes.

The pathophysiology of chronic postinfection headache remains speculative and no specific treatment has been established.

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