Chronic Daily Headache: When to Suspect Meningitis

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Millions of patients see physicians each year for headache, most of which are primary headaches. However, serious secondary headaches, such as meningitis, represent about 5% of children and 1% to 2% of adults seen in the emergency department for headache. A primary care or emergency department physician may initially miss individuals with bacterial meningitis. Considering meningitis as a headache cause is important because delay in the diagnosis may have adverse consequences. A careful history and physical examination are central in identifying individuals at high risk for meningitis. This article lists information that can be obtained from the patient that may be indicative of meningitis. Performing a lumbar puncture with appropriate examination of the cerebrospinal fluid (CSF) is the key to establishing the diagnosis of meningitis. This article also includes the types of meningitis that should be considered when the CSF demonstrates a pleocytosis.

Introduction

Headaches are common in children and adults. Prevalence studies estimate that 80% to 90% of the population experience at least one headache in their lifetime, and about 75% have experienced a headache in the preceding year [1,2]. Twenty percent to 45% of patients characterized at least one of their headaches as unbearable, and 15% saw a physician for a severe headache in the previous year. This totals more than 14 million individuals per year visiting a doctor with the complaint of headache [3]. Patients presenting to the emergency department with headache represent 2% to 4% of all patients seen [4].

Most of these individuals seek medical care for a benign headache that is either a primary headache (usually migraine) or non-serious secondary headache. However, serious secondary headaches occur. Several articles review the general approach regarding the history and examination of a patient with headache [5,6]. Our article focuses on when to consider meningitis in the patient with headache.

Typical Meningitis Characteristics

The term meningitis refers to inflammation of the meninges. Infectious agents, blood, or other foreign compounds trigger the inflammation. Causes of meningitis include infectious agents, subarachnoid hemorrhage from head trauma, vasculitis, connective tissue diseases, sarcoidosis, drugs or chemicals that induce meningitis, antigen leakage of central nervous system (CNS) tumors into the cerebrospinal fluid (CSF), and leptomeningeal cancer metastases [7•].

The incidence of meningitis is difficult to determine because many causes of meningitis are not reportable to state or national reporting systems. In the United States, rough estimates range from 200,000 to 400,000 cases per year. That figure represents 3% of patients presenting to physicians for headache and compares favorably with the actual experience of emergency departments [4,8].

The classic triad for meningitis is fever, stiff neck, and headache. The typical headache develops over a few hours with maximum intensity described as the "worst headache ever." However, the headache may be mild to moderate for those with chronic meningitis. The pain quality may be dull or pounding (similar to migraine) and diffusely, frontally, or occipitally located. Nausea, vomiting, and photophobia are common. Patients with early meningitis have relative preservation of their mental status, but the headache usually prevents a fully normal cognitive examination. Although nuchal rigidity has been considered classic for meningitis, it is present only in 50% of patients [9]. Even fever is absent in 15%. Thus, no single or set of signs and symptoms is pathognomonic for meningitis. Consequently, bacterial meningitis is initially missed in 10% to 25% of patients in the emergency department, and 30% to 50% in a physician's office [10].

Patients with meningitis have abnormal CSF containing a pleocytosis ranging from 20 to more than 5000 leukocytes/mm^3 [7•,11••]. Depending on the etiology, there may be mononuclear or neutrophil predominance. Erythrocytes are seldom present in the CSF unless the

inflammatory process damages meningeal blood vessels. CSF glucose is normal or low (< 40 mg/dL) depending on the etiology, and the protein has a mild to marked elevation (60–1000 mg/dL) depending on the cause. The etiologic agent often can be isolated from CSF by culture, identified by polymerase chain reaction (PCR) detection of nucleic acid fragments of infectious agents, seen on Gram's stain of CSF sediment, or demonstrated by serologic antibody tests.

Neuroimaging is usually normal in acute meningitis, such as viral meningitis, and in some bacterial, fungal, and parasitic meningitis. Neuroimaging in chronic meningitis is frequently abnormal and often demonstrates hydrocephalus or enhancement of the meninges around basal cisterns when a contrast agent is administered. In noninfectious causes of meningitis, blood may be seen in the subarachnoid space or brain parenchyma, and masses in the meninges may be seen.

Unusual Primary Headache Characteristics that May Mimic Meningitis

More than 90% of headache patients suffer from primary headaches, mainly migraine with or without aura and tension-type headache [12,13]. Patients with a severe migraine headache may experience nausea, vomiting, photophobia, and phonophobia, features also found in meningitis. Migraine visual phenomena usually consist of a scintillating scotoma (photopsia or flashing lights) that appears to the patient in one or both eyes as zigzag lines that persist when the eyes are closed and are usually familiar to the patient. These types of visual phenomena are not seen in meningitis unless the meningeal inflammation triggers a migraine in the patient. The neurologic examination and standard laboratory findings are usually normal in the patient with a primary headache, and important abnormal findings on neuroimaging occur in less than 0.5% of patients [14].

However, several types of migraine headache are challenging to distinguish from meningitis. The patient with chronic migraine who experiences a migraine episode with complications may have a headache plus focal neurologic signs such as weakness of the arm, leg, or face; aphasia; or difficulty in speaking, confusion, vertigo, or ataxia. Confusional migraine often affects children; these patients present with inattention, distractibility, and difficulty maintaining speech and other motor activities [15]. Patients may develop a basilar-type migraine with vertigo, hemianopia, tinnitus, diplopia, nausea and vomiting, ataxia, and other brainstem signs that typically last 1 hour but occasionally persist for several hours [16•]. Patients with these unusual migraines may have an abnormal neurologic examination, with confusion, nystagmus, ataxia, loss of vision on one side, dysarthria, or trouble speaking. However, fever, frank meningismus, papilledema, and increased leukocyte level are rare.

Chronic primary headache patients usually have a normal neurologic examination, no papilledema, and lack systemic signs of fever, adenopathy, and nuchal rigidity (although the posterior neck muscles may be tender to palpation). Diagnostic tests such as cranial CT scan rarely show pathology.

Headache Characteristics Suggesting Possible Meningitis

In most headaches, only a careful history and physical examination are required to establish the diagnosis [17,18••]. However, 5% to 9% of children and 1% to 3% of adults presenting to emergency departments with headache have meningitis [19,20]. The challenge is to identify headaches that require more extensive evaluation with blood tests, CSF analysis, and neuroimaging. Table 1 lists headache characteristics and unusual patients that require special attention.

History and Work-up

For new or worsening headaches, the history often gives helpful clues. Does the patient have predisposing conditions that could cause meningeal inflammation, such as preexisting systemic infection, immunosuppression, other family members or friends who are ill, recent foreign travel, recent seizures, consumption of medications that could trigger a chemical meningitis, neurologic problems that predate the headache, known cancers, or history of prior meningitis, prior CNS surgery, or indwelling CNS catheters? Is the headache of sudden onset or worsening over days? On general physical examination, does the patient have fever, adenopathy, new rashes, productive cough, or evidence of other systemic disease? Does neurologic examination reveal a stiff neck, stupor or coma, papilledema, cranial nerve palsies, or focal neurologic signs?

Once the decision is made to extend the work-up to exclude meningitis, useful early blood tests include leukocyte count, erythrocyte sedimentation rate, and C-reactive protein, which are often increased in meningitis. Blood cultures are positive in about 50% of patients with pyogenic meningitis but rarely positive in other types of infectious meningitis.

The diagnosis of meningitis is established from analysis of CSF. The question as to whether to obtain neuroimaging first often arises from concern that CNS masses could trigger brain herniation after the lumbar puncture. Although the actual risk of brain herniation is unknown, numerous clinical studies done before and after the advent of neuroimaging have found the risk to be low even in the presence of brain masses and increased intracranial pressure [11••]. The downside to first obtaining a CT scan before the lumbar puncture is that neuroimaging usually delays administration of antibiotics by up to 4 hours [21]. This time delay can be important if the

Table 1. Characteristics of headache indicative of possible meningitis

Unusual settings such as immunosuppression (AIDS, receiving corticosteroids or other immunosuppressive medications) or poorly controlled diabetes mellitus
Seasonal or geographic clusters, such as outbreak of viral meningitis or group exposure to fungal spores or parasites such as *Taenia solium* ova
History of prior meningitis, neurosurgical procedures, or CNS disease
History of active cancer, especially metastatic
History or clinical findings suggestive of vasculitis, arteritis, or collagen vascular disease
Recent infection such as endocarditis, osteomyelitis, pneumonia, urinary tract infection, or diarrhea
History of otitis media, mastoiditis, acute sinusitis, parameningeal infections, acute-angle glaucoma, or iritis
Recent travel to or illness in foreign country
Recent head trauma (within 3 days), even if mild
Signs of systemic infection such as fever, new rash (possible meningococcal or Lyme meningitis), adenopathy, and productive cough (possible tuberculosis)
Neurologic signs (except visual aura) that include stupor, coma, cranial nerve palsies (diplopia, facial weakness, loss of facial sensation, and vertigo), papilledema, hemiparesis, aphasia, ataxia, hemianopia, tremors, and seizures (within 72 hours)
Current laboratory tests pointing to systemic infections, such as increased leukocyte count, erythrocyte sedimentation rate, or C-reactive protein
Use of certain medications, devices, or procedures, such as trimethoprim/sulfamethoxazole, biologicals such as monoclonal antibodies, intrathecal injections, indwelling CNS catheters or shunts, or recent intracranial surgery
Headache in young child
New headache in elderly (after age 60 years)
Headache that is very different from patient's usual headache
New persistent headache, marked worsening of persistent headache, or marked change in character of chronic headache

CNS—central nervous system.

patient has bacterial meningitis because time delays are associated with an adverse clinical outcome. If bacterial meningitis is suspected, one can eliminate the time delay by administering empiric antibiotics before the patient is sent to the CT scanner [22].

Even if the CT is obtained first, it is often normal even if there is increased intracranial pressure from the meningitis [23]. The highest risk for brain herniation appears to come from intracranial masses that cause a brain shift, obstructive hydrocephalus, and severe brain edema producing highly increased intracranial pressure. Thus, we endorse obtaining prior neuroimaging in headache patients with any of the following characteristics because these patients have an increased likelihood of serious abnormalities identified on CT: papilledema, stupor or coma, focal neurologic signs, immunosuppression from disease or drugs, and advanced age. Table 2 presents the major types of meningitis, or conditions that mimic meningitis, that present with the chief complaint of headache.

Viral Syndrome or Systemic Illness Headache

Patients with acute viral syndromes or systemic illnesses represent the highest incidence of clinical conditions suspicious for meningitis. Emergency departments list viral syndrome as representing about 2% of headaches seen and 30% of secondary headaches seen [4]. However, in pediatric emergency rooms, viral syndromes represent 30% to 60% of all headaches [8,19,20]. The typical patient is often a child or young adult who has an acute viral upper respiratory syndrome, such as influenza. Individuals often present with fever, intense headache (that may be pounding), and meningismus [18••]. Lethargy, nausea, vomiting, and photophobia are common. The systemic illness may cause cough, sore throat, earache, or sinusitis. The meningismus may be prominent and worrisome for meningitis. However, patients will lack papilledema and focal neurologic signs. Because systemic bacterial and viral infections can cause meningitis, the physician usually should perform a lumbar puncture. In the viral syndrome, opening pressure is normal, as are the CSF tests ruling out meningitis.

Viral Meningitis

Viral meningitis occurs mainly in children and young adults, especially in the summer and fall. The incidence ranges from 10 to 20/100,000/year in adults, whereas it has been reported as high as 700/100,000/year in children. At pediatric emergency departments, it accounts for 5% to 9% of summer visits for headache [18••]. Children tend to present to physicians early in the illness with fever, headache, and often a stiff neck [24••]. The leukocyte count may be mildly

Table 2. Types of meningitis, or conditions that mimic meningitis, that cause headache

Viral syndromes or systemic illnesses
Influenza, systemic viral infections, infectious mononucleosis, upper respiratory illness, otitis media, pharyngitis, and pneumonia
Viral meningitis
Enterovirus meningitis
Herpes simplex type 2 meningitis
Mumps (in developing countries without widespread use of mumps vaccine)
Arbovirus meningitis (West Nile encephalitis, St. Louis encephalitis, tickborne encephalitis, Western equine encephalitis, and Eastern equine encephalitis)
Bacterial meningitis
Pyogenic bacteria
Borrelia burgdorferi (Lyme disease)
Treponema pallidum (meningovascular syphilis)
Fungal meningitis
Cryptococcus neoformans (most common but others occur)
Tuberculous meningitis
Parasitic meningitis
Meningeal neurocysticercosis
Drug-induced meningitis
Trimethoprim/sulfamethoxazole, sulfasalazine, biologics that use monoclonal antibodies, intravenous gammaglobulin
Systemic or immunologically mediated diseases
Giant cell arteritis, temporal arteritis, sarcoidosis, systemic lupus erythematosus, rheumatoid arthritis, cranial arteritis, granulomatous arteritis, Sjogren's syndrome, post-infectious syndromes, and paraneoplastic syndromes
Neoplastic meningitis
Leukemia, lymphoma, metastatic carcinomas, craniopharyngioma, teratoma, medulloblastoma, and dermoid or epidermoid cyst

low, normal, or slightly elevated. The key to the diagnosis lies in the CSF analysis, which typically shows a lymphocytic pleocytosis, normal glucose, normal to mildly elevated protein, and negative Gram's stain of CSF sediment. Occasional children have a transient pleocytosis of neutrophil predominance for up to 1 day or slightly low CSF glucose level. The most common cause of viral meningitis is an enterovirus that can be diagnosed by an enterovirus CSF PCR assay [24••]. In young sexually active adults, herpes simplex virus (HSV) type 2 meningitis often occurs as a primary meningitis or as a recurrent meningitis and can be diagnosed by a herpes simplex CSF PCR assay [25]. Mumps meningitis is common in developing countries that do not routinely administer the mumps vaccine to children. The prognosis is excellent for patients with viral meningitis.

Bacterial, Fungal, Tuberculous, and Parasitic Meningitis

Bacterial meningitis is the most common of these uncommon forms of infectious meningitis and has an estimated incidence in developed countries of 3 to 6/100,000 adults/year [26,27]. In bacterial meningitis, the classic signs of fever, headache, neck pain, and altered mental status were found in only two thirds of patients [28]. Fever and neck stiffness were almost always present, headache was common, but altered mental status was found in only one fifth. Headache alone without any of the other classic signs correlates highly with the patient not having bacterial meningitis. Fungal, tuberculous, and parasitic meningitis usually present with a persistent headache that is worsening from the subacute or chronic meningitis [7•].

Unfortunately, if the diagnosis of these types of meningitis is missed, resulting in a delay before appropriate antibiotics are administered, the outcome can be much worse. Again, lumbar puncture is the key to the diagnosis. The CSF leukocyte count in bacterial meningitis usually has a neutrophil predominance, whereas fungal and tuberculous meningitis may show a mixed neutrophil-mononuclear or even a mononuclear predominance. CSF cultures, PCR assays, and serologic tests establish the etiology.

Recurrent Meningitis

Recurrent meningitis is uncommon but can be confused with recurrent primary headaches. Over 90% of cases

of recurrent meningitis are due to HSV (95% of cases from HSV-2 and 5% from HSV-1) [29]. These patients are young adults (mean age 37 years) with a slight female predominance who experience benign recurring episodes of fever, severe headache, photophobia, and meningismus lasting 2 to 5 days followed by spontaneous recovery. Less than 50% of the patients recall experiencing genital herpetic lesions. The total number of episodes ranges from three to nine, with the time to recurrence varying from weeks to months or years. Over time, the recurrences become less common.

About 5% of patients with recurrent meningitis have other etiologies. These patients often have an abrupt onset with a severe diffuse headache that can last days to weeks. The more common causes include repeated exposures to drugs or biological products that trigger aseptic meningitis, intracranial and intraspinal tumors and cysts that periodically leak antigenic material into the CSF, and systemic connective tissue diseases [7•,25].

Drug-induced Meningitis

A history of current medications taken by the headache patient occasionally points to the cause of the headache and meningitis. Although there is a long list of drugs that have been reported to trigger acute drug-induced meningitis, three types of medications are particularly common: trimethoprim/sulfamethoxazole, biologicals that use monoclonal antibodies, and intravenous gammaglobulin [30]. The headache and meningismus onset usually occur 1 to 2 days after the drug is administered. Patients often have fever, nausea, and malaise. Lumbar puncture shows a leukocyte pleocytosis that may have a neutrophil predominance, normal glucose, and usually a normal protein level. The meningitis subsides over a few days but may recur when the same drug is taken again.

Neoplastic Meningitis

Neoplastic meningitis (also called carcinomatous meningitis, leptomeningeal metastases, or lymphomatous meningitis) is an important category to consider in patients with chronic headaches [7•]. About 5% of patients with extraneural cancer have spread of malignant cells to the meningeal space. Even this small percentage becomes quite relevant because over 1 million cases/year of cancer are diagnosed in the United States [31•]. Statistically, the most common cancer types seen in neoplastic meningitis are breast, lung, melanoma, and leukemia. Cancer cells reaching the meninges spread via CSF and gravity. Thus, the most common sites of pathological involvement are the base of the brain (basilar cisterns or posterior fossa) and base of spine (cauda equina).

Clinical signs and symptoms depend on the tumor location and whether the metastases are causing hydrocephalus [31•]. Patients often complain of a dull persistent headache that is slowly worsening. If hydrocephalus develops, the headache becomes more intense. In addition, posterior fossa metastases commonly cause cranial nerve palsies and ataxia. Patients with hydrocephalus experience worsening headaches, nausea/vomiting, encephalopathy, and papilledema. Nuchal rigidity is present in only 15% of cases. Although fever is uncommon, these patients may demonstrate systemic signs depending on the origin of the tumor. Cranial enhanced CT is abnormal in 25% to 50%, but MRI with gadolinium demonstrates abnormalities in more than 75% of patients.

The CSF usually is abnormal, with a pleocytosis and increased protein. Lymphocytes are often present, along with malignant cells. A firm diagnosis is established by identification of malignant cells on cytologic examination of CSF or by meningeal biopsy [31•]. Unfortunately, negative CSF cytology in cases of proven neoplastic meningitis ranges from 25% to 40%.

Worrisome Headaches in the Elderly

The prevalence of headaches decreases in the elderly, but individuals aged 65 to 74 years still have a 1-year headache prevalence of 57% [32]. However, the incidence of secondary headaches increases. It can be challenging to identifying a headache caused by meningitis because the patient may not have fever and may present with vague symptoms. It is often difficult to distinguish meningismus from the patient's chronic stiff neck caused by cervical arthritis. Elderly patients often have comorbid chronic neurologic illnesses that produce a variety of confounding signs and symptoms [33••].

Attention should be paid to the following diseases that often present with a chronic secondary headache: head trauma with subarachnoid hemorrhage or subdural hematoma, giant cell arteritis, herpes simplex or arbovirus meningoencephalitis, and neoplastic meningitis [33••]. Other non-meningitis causes of headache include brain tumors, toxins (eg, carbon monoxide), medication side effects (eg, vasodilators taken for angina), acute-angle glaucoma, and stroke. When meningitis is suspected, it is prudent to obtain neuroimaging before performing the lumbar puncture due to the increased prevalence of CNS masses.

Conclusions

Most, but not all, headaches are primary headaches (migraine or tension-type headache). The challenge for the clinician evaluating a child or adult with headache is determining how suspicious he or she should be regarding possible meningitis. Table 1 presents characteristics of headache that are indicative of possible meningitis. When these warning signals appear, one should entertain the diagnosis of meningitis and consider a lumbar puncture and possibly neuroimaging. Table 2 lists the types of meningitis, or conditions that mimic meningitis, that cause

headache. However, meningitis can only be firmly diagnosed by examining the patient's CSF. Treatment depends on the etiology of the CSF inflammation.

Disclosures

No potential conflict of interest relevant to this article was reported.

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