

REVIEW ARTICLE

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Chronic Meningitis

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IN HIS 1987 EDITORIAL IN THE JOURNAL, IN WHICH HE COMMENTED ON AN article about serologic testing of cerebrospinal fluid (CSF) in the diagnosis of meningeal sporotrichosis, Dr. Morton Swartz suggested that there are “many causes to consider” when clinicians are confronted with the problem of chronic meningitis.¹ Since that time, the list of causes of chronic meningitis, as well as diagnostic tests and treatments, has expanded, making evaluation and treatment even more complex. The generally accepted definition of chronic meningitis is inflammation of the meninges, with signs and symptoms persisting for at least 4 weeks without alleviation.²

New pathogens have been added to the list of infectious causes of chronic meningitis, and molecular analysis now provides the means to detect them.³ Next-generation sequencing allows pathogens to be identified without the bias of a predetermined result.⁴ In addition, as a result of long-term immunosuppressive therapy, opportunistic infections such as cryptococcal meningitis (accounting for 3400 hospitalizations annually in the United States)⁵ have become about as common as bacterial meningitis (accounting for 3600 cases per year).⁶

This brief review references previous knowledge of chronic meningitis and introduces current approaches to the disorder. It considers entities involving the leptomeninges or pachymeninges but not the brain parenchyma, since inflammation in the brain parenchyma would properly be called encephalitis. However, many inflammatory diseases affect the meninges and parenchyma simultaneously (meningoencephalitis).

CLINICAL MANIFESTATIONS

Symptoms of chronic meningitis include headache, lethargy, mental status changes, and fever. The headache is typically constant but nonspecific in location, quality, and temporal pattern. Progressively worsening headache, especially with mental clouding, and fever should prompt consideration of lumbar puncture to detect the inflammatory formula in CSF that characterizes chronic meningitis. Cranial-nerve dysfunction such as hearing loss or diplopia can also point to chronic meningitis, since these nerves are affected in their course through the subarachnoid space. Cognitive changes occur in approximately 40% of patients with chronic meningitis,⁷ with the incidence varying according to the cause. In some cases, cognitive change is the sole presenting feature, which makes chronic meningitis part of the differential diagnosis in patients with rapidly progressive dementia, particularly those with a history of immunosuppression. Nuchal rigidity occurs less commonly in chronic meningitis than in acute or subacute meningitis and occurs even less commonly with noninfectious causes than with infectious causes. For example, in a review of neurosarcoidosis, 65 of 83 patients had chronic meningitis, none with

signs of meningeal irritation and nuchal rigidity.⁸ Inflammatory leptomenigeal changes may cause hydrocephalus and elevated intracranial pressure, particularly in cryptococcal meningitis. Seizures or strokelike episodes can occur as a result of infectious or inflammatory cerebral vasculitis. The inflammatory process may affect the cranial nerves and nerve roots in the subarachnoid space and can cause cranial neuropathies or radiculopathies.

DIFFERENTIAL DIAGNOSIS

INFLAMMATORY, NEOPLASTIC, CHEMICAL, AND OTHER NONINFECTIOUS CAUSES

Chronic meningitis is broadly characterized as infectious or noninfectious (Table 1). Geographic region of residence, travel, immune status, and underlying illnesses are the initial building blocks for the differential diagnosis. Systematic examination of the lungs, skin, liver, spleen, joints, eyes, and lymph nodes provides information regarding inflammatory and granulomatous diseases that often underlie chronic meningitis. For example, uveitis suggests sarcoidosis, lymphoma, Behçet's disease, or the rare category of idiopathic "uveo-meningeal syndromes."⁹ Rheumatoid arthritis and sarcoidosis can cause inflammatory reactions in the meninges, but they also confer a predisposition to meningitis with opportunistic infections. Tumors or cysts in the neuraxis can induce chemical meningitis by leaking chemical contents into the CSF, as occurs with dermoid cysts or craniopharyngiomas. Parameningeal infections and inflammatory reactions of varied sources cause a sterile inflammatory response in the CSF and are manifested as chronic meningitis. Many cases previously thought to be idiopathic pachymeningitis are now understood to be due to IgG4 disease or rheumatoid arthritis involving the meninges.¹⁰

INFECTIOUS CAUSES

As a predicate to diagnosis, it is helpful to be acquainted with infectious organisms that are endemic in the patient's geographic region and are capable of causing chronic meningitis. In areas where tuberculosis is endemic, empirical antituberculosis treatment is often initiated before the diagnostic evaluation of meningitis has been completed. Coccidioidomycosis is endemic

in the southwestern United States, and histoplasmosis and blastomycosis (Fig. 1B) are endemic in the upper Midwest and the Ohio and Mississippi River valleys. *Cryptococcus gattii*, which has appeared on the Pacific Coast, can cause chronic meningitis in nonimmunosuppressed patients.¹¹ In the northeastern United States and the upper Midwest, Lyme disease is a diagnostic consideration in cases of chronic meningitis. Cryptococcal meningitis is currently the most common cause of chronic meningitis in immunocompromised persons and persons with human immunodeficiency virus (HIV) infection. Patients with agammaglobulinemia and those receiving B-cell-depleting immunotherapy are susceptible to chronic enteroviral meningitis. Contaminated glucocorticoids used for epidural injection caused an outbreak of chronic fungal meningitis in 2012 in the United States.^{12,13} Consulting local public health departments can be useful in understanding unexplained outbreaks of chronic meningitis. Patients with a history of neurosurgical treatment, placement of a ventriculoperitoneal shunt, otic surgery, or diabetes are predisposed to both bacterial and fungal causes of chronic meningitis. Selected causes of chronic meningitis are listed in Table 1. A comprehensive list of all the causes would be too long to enumerate here.

IMAGING

Advances in imaging of the head have allowed for the detection of leptomeningitis (affecting the pia, arachnoid, and CSF-filled subarachnoid space) and pachymeningitis (affecting the dura mater) and for the distinction between the two.¹⁴ Cranial and spinal imaging is also necessary to identify focal and parameningeal infections that cause a sterile chronic meningeal reaction.

A computed tomographic (CT) scan of the head can be used to rule out a mass that may be causing a sterile meningitis. It can also be used for the detection of hydrocephalus and mass effect before lumbar puncture is performed, and although CT imaging performed for this purpose may show enhancement of the meninges and provide reassurance regarding the safety of lumbar puncture, it is not helpful in establishing the cause of chronic meningitis. Magnetic resonance imaging (MRI) of the head with contrast material may be normal in chronic meningitis or

Table 1. Types of Chronic Meningitis According to Cause.***Infectious causes****Bacterial**

Mycobacterium tuberculosis
Listeria monocytogenes
Borrelia burgdorferi
Treponema pallidum
 Leptospira species
 Brucella species
 Nocardia species
Tropheryma whipplei
 Pseudomonas species

Fungal

Cryptococcus neoformans and *C. gattii*
Histoplasma capsulatum
Blastomyces dermatitidis
Coccidioides immitis
Sporothrix schenckii
 Aspergillus
 Candida species

Parasitic

Taenia solium (referred to as racemose form)
Angiostrongylus cantonensis
Toxoplasma gondii

Viral

HIV
 Chronic enterovirus

Neoplastic causes

Meningeal carcinomatosis
 Meningeal lymphomatosis
 Leukemic infiltration
 Meningeal gliomatosis
 Other primary CNS tumors (e.g., ependymoma, germinoma)

Causes of chemical meningitis

Craniopharyngioma
 Dermoid or epidermoid cyst

Autoimmune causes

Granulomatosis with polyangiitis
 Rheumatoid arthritis
 Sjögren's syndrome
 Still's disease
 Primary CNS angiitis
 IgG4 disease
 Idiopathic hypertrophic pachymeningitis
 Neurosarcooidosis
 Neurologic Behçet's disease
 Vogt-Koyanagi-Harada disease

Parameningeal infectious causes

Chronic epidural abscess
 Chronic osteomyelitis of the skull or vertebrae

* CNS denotes central nervous system, and HIV human immunodeficiency virus.

may show hyperintensity in the cerebral sulci and basal cisterns on T2-weighted, fluid-attenuated inversion recovery imaging. After the administration of contrast material, imaging frequently shows abnormally enhancing basilar subarachnoid spaces and leptomeningeal membranes (Fig. 1). Hyperintensity in the cerebral sulci may be seen on diffusion-weighted imaging but is nonspecific for infectious meningitis. Enhancement in the dura reflects pachymeningitis and directs attention to infections that involve the dura, such as granulomatous disorders and IgG4 pachymeningitis.¹⁴ Smooth and diffuse enhancement of the dural membranes, without leptomeningeal enhancement, may indicate intracranial hypotension due to spontaneous CSF leak or may have been induced by a recent lumbar puncture and is sometimes confused with the imaging features of chronic meningitis.^{15,16} Neuroimaging with MRI of the head is also used for selecting a site for brain biopsy, if needed for the diagnosis of chronic meningitis.

DIAGNOSTIC EVALUATION AND TESTING

The CSF cell count is elevated, almost by definition, in chronic meningitis, but there are exceptions in persons with severe immunosuppression or in some forms of neoplastic meningitis.^{17,18} There is generally a lymphocyte-predominant pleocytosis because of the chronic nature of the disorder. However, tuberculous meningitis and some other infections, including nocardia, brucella, and fungal infections, may be characterized by persistent neutrophilic meningitis, and that CSF pattern is a hint to their presence.¹⁹ Chronic neutrophilic meningitis has also been described in autoimmune disorders such as Still's disease²⁰ and in cases without an identified cause. Eosinophils may indicate parasitic or coccidioid meningitis. The CSF protein concentration is nearly always elevated, but this finding is nonspecific. Hypoglycorrhachia commonly accompanies infectious (and some noninfectious) causes of chronic meningitis, including sarcoidosis and meningeal metastases, but the CSF glucose concentration may be normal with other causes.

Table 2 provides a suggested approach to the diagnosis of chronic meningitis. High-volume CSF sampling (10 to 20 ml per sample) may increase diagnostic sensitivity for tuberculous and

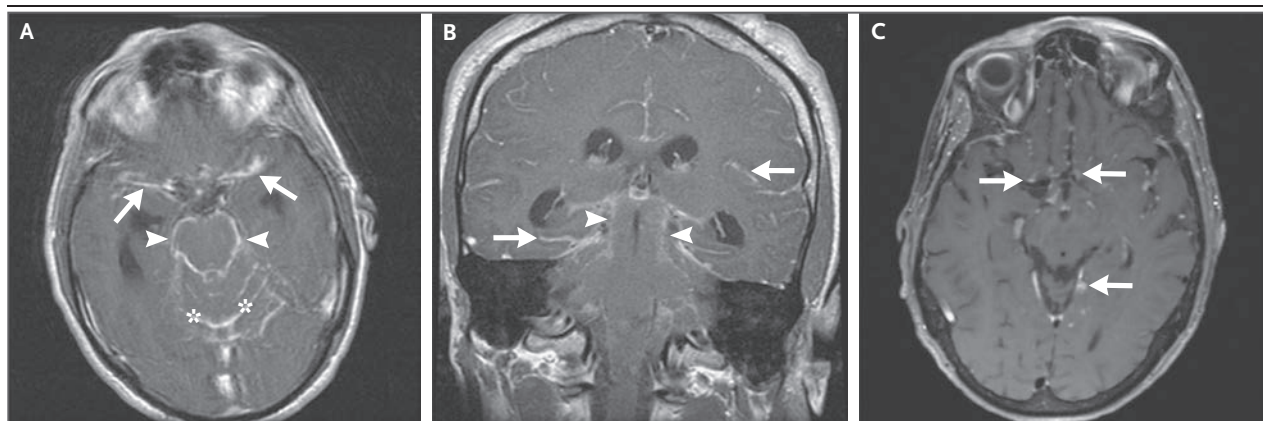


Figure 1. T1-Weighted MRI of the Head Showing Leptomeningeal Enhancement.

Panel A shows a contrast-enhanced axial image from a patient with chronic meningitis caused by blastomycosis. There is leptomeningeal enhancement in the basilar cistern around the brain stem (arrowheads), in the sulci of the folia of the cerebellum (asterisks), and in the perivascular subarachnoid space of the middle cerebral arteries (arrows). Panel B shows a contrast-enhanced coronal image from a patient with chronic tuberculous meningitis. There is leptomeningeal enhancement in the cortical sulci (arrows) and along the surface of the brain stem (arrowheads). Panel C shows a contrast-enhanced axial image from a patient with chronic meningitis caused by neurosarcooidosis. There are multiple small, nodular, contrast-enhanced lesions (arrows) in the leptomeninges in the inferior frontal brain surface and edge of the tentorium cerebelli.

fungal meningitis. Blood and CSF serologic tests (e.g., the Lyme disease antibody index)²¹ and positron-emission tomography for occult systemic disorders may provide useful information in otherwise obscure cases.

A mycobacterial polymerase-chain-reaction (PCR) assay of CSF for tuberculosis has an estimated sensitivity of close to 95% with the use of newer techniques.²² The absence of a blood interferon- γ reaction against mycobacterial antigens does not rule out tuberculosis as a cause of meningitis. Three spinal taps over a period of several days for difficult-to-culture organisms (fungi and *Mycobacterium tuberculosis*) are usually sufficient to rule out these diagnoses. A β -D-glucan assay of CSF may be a useful adjunct for identifying fungal infections from candida or exserohilum in patients with negative cultures or negative specific antigen tests.^{23,24} Galactomannan testing in the CSF has been positive in some cases of aspergillus meningitis.²⁵ For situations in which clinical decisions about initiating or continuing antibiotic therapy will be affected, PCR for the bacterial 16S ribosomal RNA (rRNA) gene can be performed in some laboratories.²⁶ Sequencing from an amplified product may identify the organism.²⁷ Likewise, if a fungal infection is considered likely, PCR testing for 18S rRNA can be performed in some laboratories.²⁸

Two large-volume taps for cytologic studies

are typically considered sufficient to detect neoplastic meningitis.²⁹ A detailed evaluation of HIV status and further evaluation of the immune state may be warranted when an opportunistic pathogen is identified as the cause of meningitis. Defects in cell-mediated immunity and immunoglobulin deficiencies are associated with infectious chronic meningitis. Quantitation of B cells and T cells, with analysis of subsets, and immunoglobulin subset quantitation may help to guide decisions regarding the choice and duration of treatment.

NEWER DIAGNOSTIC AIDS

Many U.S. laboratories now use a commercially available, multiple-organism PCR test of CSF for the diagnosis of acute meningitis and encephalitis.³⁰ However, these techniques are considered to be less useful for chronic meningitis. Chronic enteroviral meningoencephalitis may be the exception, since it is difficult to identify without this testing. Although these CSF panels test for cryptococcus (*C. neoformans* and *C. gattii*), their sensitivity is 52%,³¹ as compared with a sensitivity of 90 to 95% with a stand-alone test for cryptococcal antigen.³²

Newer methods of microbiologic diagnosis using metagenomic or next-generation sequencing do not limit identification to specific organ-

Table 2. Evaluation for Chronic Meningitis.***Tests to be performed in all patients in whom chronic meningitis is suspected**

Spinal tap — up to three times for fungal and mycobacterial cultures, if initially negative

CSF cytologic evaluation — twice, if initially negative

CSF test for cryptococcal antigen

CSF bacterial culture

CSF protein and glucose measurements and cell count

CSF serologic tests for syphilis and fungal infections (histoplasmosis, blastomycosis, or coccidioidomycosis, depending on epidemiologic features)

MRI of the head with gadolinium

Serum serologic tests for syphilis, HIV infection, Lyme disease

Chest CT scan (for lymphadenopathy, granuloma, or neoplasm)

PPD skin test or interferon- γ release assay for tuberculosis

Additional tests to consider performing

Serum serologic tests for toxoplasma, brucella, leptospira

CSF serologic test for sporothrix

CSF test for fungal antigens (histoplasma, blastomyces)

CSF fungal PCR assays (histoplasma, blastomyces, aspergillus)

CSF β -D-glucan test for fungal antigens (candida, exserohilum, other fungi)

CSF galactomannan test for aspergillus antigen

CSF PCR assay for enterovirus

Serum ENA, ANCA, CCP antibodies

CSF PCR assay for tuberculosis

CSF PCR assay for Whipple's disease

CSF serologic test for Lyme disease and Lyme disease antibody index

Ophthalmologic examination for uveitis

Whole-body PET scan

CSF metagenomic sequencing for infectious agents

Dural, leptomeningeal, or brain biopsy targeted by imaging

* ANCA denotes antineutrophil cytoplasmic antibody, CCP cyclic citrullinated peptide, CSF cerebrospinal fluid, CT computed tomography, ENA extractable nuclear antigen, MRI magnetic resonance imaging, PCR polymerase chain reaction, PET positron-emission tomography, and PPD purified protein derivative.

isms; rather, they provide sequencing information for any bacterial, fungal, or viral nucleic acid in the CSF.³³ The sensitivity and specificity of next-generation sequencing in the evaluation of chronic meningitis are still being determined; a study involving seven patients with puzzling cases of chronic meningitis identified *Taenia solium*, HIV, cryptococcus, aspergillus, histoplasma, and candida, although no conclusion can be drawn about the diagnostic sensitivity of this technique in a broader population of patients with chronic meningitis.⁴ A study of metage-

omic sequencing in CSF specimens obtained at the Mayo Clinic from 53 patients in whom there was uncertainty about the diagnosis and 27 externally referred specimens over a 2-year period, the rate of diagnostic detection of an organism was only 15%, and more than half the detected infections were considered to be inconsistent with the clinical presentation.³⁴ The technology requires complex computational abilities and, although expensive, is potentially cheaper than imaging and brain biopsy. Even though the obstacles to the use of next-generation sequencing are not insurmountable, it cannot yet be recommended for routine initial use in evaluating chronic meningitis.

BRAIN BIOPSY

In a patient with chronic meningitis, progressive neurologic decline, and inconclusive systemic and CSF evaluations, brain and meningeal biopsy may be considered to establish the diagnosis. There is little information about the yield of brain biopsy in a range of patients with chronic meningitis. In a 1994 retrospective, single-center study involving 37 patients who had undergone extensive evaluations short of biopsy, half of whom had abnormalities of the leptomeninges on MRI, biopsy specimens from nonenhancing brain or meningeal regions provided a diagnosis in only 9% of the patients.³⁵ However, a diagnosis was obtained in 80% of the patients with biopsy of an enhancing region. A second biopsy was diagnostic in three of four cases. Even in nondiagnostic cases, a generic pathological change can offer guidance regarding empirical therapy. Granulomatous characteristics, rather than a vasculitic abnormality, might point toward a trial of drugs for neurosarcoid rather than vasculitis treatment. Necrotizing granuloma might prompt a trial of antituberculosis or antifungal therapy, depending on the clinical circumstances. Chronic meningitis eludes diagnosis, despite exhaustive testing, in a large but uncertain proportion of patients.

EMPIRICAL TREATMENT OF CHRONIC MENINGITIS

If no diagnosis has been established after non-invasive testing or even after brain biopsy, the choice of empirical treatment is generally anti-

tuberculosis therapy, antifungal therapy, or glucocorticoids. Empirical antibiotic therapy is not recommended unless a history of exposure or other information suggests the presence of a responsive organism. In regions where tuberculosis is prevalent, empirical antituberculosis therapy is considered reasonable if cryptococcal meningitis has been ruled out. Antituberculosis therapy is not recommended empirically in every such case; sometimes a trial of glucocorticoids is initiated when there is greater suspicion about neurosarcoidosis than about tuberculosis. Even in a 1987 study in the United States, involving 83 patients with chronic meningitis, 40% were ultimately found to have tuberculous meningitis.³⁶ Concurrent glucocorticoid therapy is recommended for tuberculous meningitis in some instances, but if tuberculosis cannot be identified, glucocorticoids may be disadvantageous because they obscure the reduction in the CSF cellular response to empirical antituberculosis therapy. In regions where tuberculosis is uncommon, treatment with glucocorticoids alone, with follow-up clinical assessment and imaging in 4 to 8 weeks, is a reasonable approach to cases of chronic meningitis for which no diagnosis can be established despite extensive evaluation.³⁷

PROGNOSIS

No general statement about prognosis is possible, given the variety of disorders that cause chronic meningitis. In the future, improved and more widely available PCR tests, such as those that are available for tuberculosis,²² and next-generation sequencing³ may reveal more infec-

tious meningeal disorders. New autoantibodies against neuronal antigens may point to autoimmune disorders, as has occurred with meningoencephalitis and anti-glial fibrillary acidic protein astrocytopathy.³⁸

Few studies have followed patients longitudinally to assess the outcome of chronic meningitis. In a study reported in 1994, before the advent of PCR and next-generation sequencing, 49 patients with chronic meningitis, in whom the diagnosis could not be established, were followed for a mean of 50 months.⁷ The diagnosis was eventually established in 10 of the patients (8 had neoplastic meningitis, and 2 had histoplasma meningitis), and 33 of the remaining 39 patients had good outcomes despite prolonged illness. Two patients died without receiving a diagnosis. Empirical antituberculosis therapy, administered mainly in patients from the upper midwestern United States, did not appear to alter the course of illness. Our impression was that glucocorticoid therapy relieved symptoms.

CONCLUSIONS

Chronic meningitis is a challenging diagnostic entity that differs from acute meningitis with respect to causes and diagnostic process and is associated with many potential underlying infectious and noninfectious inflammatory disorders. Treatment requires diligent and persistent follow-up. As new-generation sequencing and other techniques are applied judiciously, higher rates of diagnosis may be attained.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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