Evaluation and Treatment of Chronic Meningitis

The Neurohospitalist
2014, Vol. 4(4) 185-195
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DOI: 10.1177/1941874414528940
nho.sagepub.com

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Abstract

Chronic meningitis is defined as an inflammatory cerebrospinal fluid (CSF) profile that persists for at least 1 month. The presentation often includes headache, nausea, vomiting, cranial neuropathies, symptoms of elevated intracranial pressure, or focal neurologic deficits. The most common etiologies of chronic meningitis fall into 3 broad categories: infectious, autoimmune, and neoplastic. Evaluation of the patient with suspected chronic meningitis should include a detailed history and physical examination as well as repeated CSF diagnostics, serologic studies, and biopsy of the brain or other abnormal tissue (eg, lymph node or lung), when indicated. Early identification of the etiology and rapid treatment are crucial for improving morbidity and mortality, but potential infectious and neoplastic conditions should be excluded prior to empirically starting steroids or immunosuppressive medications.

Keywords

central nervous system infections, meningoencephalitis, meningitis, encephalitis, autoimmune diseases of the nervous system

Introduction

Chronic inflammation in the cerebrospinal fluid (CSF) can be a diagnostic dilemma for the neurohospitalist. Early recognition, diagnosis, and treatment are important for improving morbidity and mortality. Chronic meningitis is commonly defined as inflammation in the CSF persisting for at least 1 month without spontaneous resolution. The differential diagnosis for chronic meningitis is long and can be divided into 3 categories: infectious, inflammatory, and neoplastic. To arrive at an accurate diagnosis, the neurohospitalist must first acquire a detailed patient history including symptomatology, time course, systemic symptoms, travel history, exposures, and factors such as intravenous drug abuse, medications, and overall immune status of the patient. These important details of the patient history will serve as a guide for determining workup and treatment.

Case Example

A 25-year-old woman presents to the emergency department with 3 weeks of headache and behavioral changes. She endorses a 12-month history of intermittent photosensitive rash and generalized arthralgias. Her family history is significant for inflammatory bowel disease. She denies recent travel, risk factors for human immunodeficiency virus (HIV) infection, insect bites, weight loss, or pulmonary symptoms. Her examination is significant for a malar rash on her face, poor attention, concentration, and abstraction with inability

to perform complex tasks. She is generally hyperreflexic without focal weakness, numbness, or cranial neuropathies. This history would suggest a probable autoimmune etiology for chronic meningitis, such as systemic lupus erythematosus (SLE) rather than an infectious or neoplastic etiology. If this same young woman was admitted after a recent respiratory illness with headache and behavioral changes, and there was a history of rock and cave climbing, the differential would be quite different and an infectious etiology such as histoplasmosis would be considered. Histoplasmosis is an organism that is transmitted via inhalation or aerosolized avian and bat populations. Infected patients may report cleaning chicken coups, cave climbing, or close proximity to excavation where soil is aerosolized.

Approach to Initial Diagnosis and Management

When clinical history and laboratory data are suggestive of chronic meningitis, the next step in workup should include neuroimaging. Magnetic resonance imaging (MRI) of the

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brain with and without gadolinium contrast is more sensitive for detecting leptomeningeal enhancement than computerized tomography (CT). In patients for whom there is suspicion for a mass occupying lesion, neuroimaging is essential prior to lumbar puncture. Following neuroimaging, the clinician should proceed with lumbar puncture to assess for inflammation in the CSF. Initial CSF testing should include measurement of opening pressure, cell count with differential, glucose, protein, bacterial culture, and Gram stain. Further testing should be tailored to potential exposures elicited during the clinic history.

Empiric Therapy

As opposed to the patient who presents acutely with signs and symptoms of meningitis who should be started on empiric antibiotics, antivirals, and steroids, patients presenting with protracted mild symptoms consistent with chronic meningitis do not necessarily warrant broad spectrum empiric coverage. In general, processes that cause chronic meningitis do not respond to traditional empiric antibiotic and antiviral treatment. The decision to initiate empiric therapy should be considered on a case-by-case basis and should consider factors such as abnormalities detected on clinical examination, immune status, recent exposures, most likely etiologies, and potential risks of treatment. A bacterial etiology of meningitis should always be considered in patients who are pregnant or patients with neutropenia or recent transplantation. Patients suspected of having acute bacterial meningitis should be treated empirically with broad spectrum antibiotics.

Approach to Infectious Causes of Chronic Meningitis

Patients with infectious etiologies of chronic meningitis may present with signs and symptoms of elevated intracranial pressure (ICP), particularly when caused by *Cryptococcus neoformans* subsp. Previously described as a disease isolated to people with HIV infection or a hematologic malignancy, fungal meningitis is now recognized in immunocompetent patients, and those with immunologic conditions receiving immunosuppressant medications or monoclonal antibodies such as rituximab. Identification of the organism causing chronic meningitis is often challenging; a proposed algorithm is shown in Figure 1. Clinicians should initially consider the underlying immune status of the patient. Typically patients will fit into 1 of the 3 categories: neutropenic, B-cell or immunoglobulin deficient, or T-cell deficient. By identifying the immunodeficiency, clinicians can narrow down the potential organisms of concern. The second step to diagnosis is incorporating the clinical history and examination. The final step is advanced neuroimaging, CSF testing, and potentially brain biopsy to confirm the diagnosis.

Case Example

A 30-year-old female with history of HIV infection, who is noncompliant with antiretroviral therapy, presents with 4 weeks of headache, vomiting, and diplopia. She lives in New York City and has daily exposure to pigeons that nest in her building. On presentation, she is afebrile with a CD4 count of 20 cells/ μ L. She has nuchal rigidity and bilateral cranial nerve 6 palsies.

In determining the etiology and treatment plan for this patient, the clinician can utilize the proposed 3-step algorithm. Step 1 is to determine the immunologic status; this patient would fall into severe T-cell deficiency. The second step is to incorporate her history of elevated ICP manifested primarily by the presence of bilateral cranial nerve 6 palsies, which would raise your concern for fungal or mycobacterial organisms that are notorious for presenting with elevated ICP. Specifically this HIV-positive patient with a CD4 count less than 50 cells/ μ L would be at risk of cryptococcal meningitis, toxoplasma encephalitis, syphilis, and tuberculous meningitis. The final step is to incorporate neuroimaging, which in this case revealed diffuse leptomeningeal enhancement with hydrocephalus; there was no evidence of mass lesion—as seen with toxoplasmosis—or of a basilar predilection for meningitis—as seen in tuberculosis (TB). Antifungal coverage was initiated with amphotericin B to cover for suspected fungal meningitis. Finally, lumbar puncture revealed opening pressure of 40 mm H₂O, 40 white blood cell/mL with a mixed monocytic and neutrophilic predominance, normal glucose, and protein of 200 mg/dL. Cryptococcal antigen was positive in the CSF, confirming the diagnosis of cryptococcal meningitis.

Infectious Causes of Chronic Meningitis

Fungal, bacterial, viral, and parasitic pathogens can invade the central nervous system (CNS) and present clinically as chronic meningitis. Increasing use of immunosuppressant medications for autoimmune disease and posttransplantation immunosuppression, as well as predisposing conditions such as impaired cellular and humoral immunity, have led to a larger population at risk of chronic meningitis. This section will review the most common causes of chronic infectious meningitis, including *Cryptococcus* species, *Aspergillus fumigatus*, *Mycobacterium tuberculosis*, and syphilis (Table 1).

Cryptococcus

Cryptococcal meningitis is most often caused by the encapsulated yeast organism *C. neoformans*, but other species of *Cryptococcus*, such as *Cryptococcus gattii*, are emerging as pathogens that can affect immunocompetent and immunocompromised people. *Cryptococcus neoformans* is primarily found in contaminated soil and avian excrement. Infection usually occurs by inhalation of the organism.¹ Cryptococcal meningitis is most common in people with

Figure 1. Approach to chronic meningitis based on immune status of the patient, clinical presentation, and neuroimaging findings. Modified from Pruitt A. CNS infections in patients with cancer. *Continuum (Minneapolis)*. 2012;18(2):384-405; Table 8-1 and Figure 8-1.

Table 1. Infectious Etiologies of Chronic Meningitis; CSF Findings, Serologic Testing, Clinical Presentation, Imaging Characteristics, and Systemic Features.

Infectious Meningitis: CSF Parameters and Diagnosis											
Organism	Opening Pressure	WBC	Differential	Glucose	Protein	CSF Diagnostic Testing	Microscopic Appearance of Organism	Pathogenesis	CNS Features	Neuroimaging	Systemic Features
Cryptococcus	↑	↑↔	Mononuclear	↓	↑	India ink staining Cryptococcal capsular polysaccharide antigen Fungal culture	Encapsulated fungi; yeast-like cells with budding daughter cells. Capsule visualized by India ink (halo effect)	Inhalation, fungemia	Basilar meningitis, granuloma, vasculitis	Hydrocephalus, cerebral edema, leptomeningeal enhancement, and cryptococcomas	Pulmonary, multiorgan involvement
Coccidioidomycosis	↑↔	↑	Early neutrophil Mononuclear Eosinophilic (70%)	↓	↑	Complement fixation antibody testing Fungal culture	Yeast form endosporeulating spherules. Branched septate hyphae with alternating arthroconidia.	Airborne, fungemia	Chronic meningitis, cerebritis, arteritis, abscess, granuloma	Hydrocephalus, meningeal enhancement, nodular enhancement, basilar meningitis, cerebral infarction.	
Histoplasmosis	↔	↑	Mononuclear	↓	↑	Histoplasma polysaccharide antigen Fungal culture Urine histoplasmosis antigen	Hyphae large macroconidia and smaller infectious microconidia. At temperatures <35°C yeast form. Hyphal elements possible.	Airborne, fungemia	Meningitis, granuloma	Normal, granuloma, meningeal enhancement	Acute or chronic pulmonary, dissemination with multiorgan
Blastomycosis	↑	↑	Early neutrophil Mononuclear	↓	↑	Fungal culture	Mycellium at room temperature; yeast phase at 37°C. Conidia, yeast cells with multinucleate broad budding.	Airborne, fungemia	Meningitis	Single or multiple abscesses, granuloma, meningeal enhancement, epidural extensions and overlying osteomyelitis	Pulmonary, cutaneous
Aspergillosis	↔	↑	Early neutrophil Mononuclear	↓	↑	CSF-PCR Antigen galactomannan Antibody Fungal culture	Septate hyphae branched at 45° angles with conidiophores. Hyphae develop terminal buds forming small conidia.	Fungemia, direct inoculation by trauma or surgery, extension from paranasal, angioinvasive	Meningitis, vasculitis, mycotic aneurysm, granuloma, abscess spinal cord involvement	Multiple abscesses, meningeal enhancement, infarction, hemorrhage, sinusitis with extension	Pulmonary
Mycobacterial	↑↔	↑	Mononuclear	↓	↑	AFB smear Culture on Lowenstein-Jensen medium PCR	Acid fast bacilli	Inhalation, hematologic dissemination	Basilar meningitis, vasculitis, abscess	Hydrocephalus, meningeal enhancement, basilar meningitis, cerebral infarction, tuberculomas	Pulmonary
Syphilis	↔	↑↔	Mononuclear	↔↓	↑	VDRL (serum and CSF) FTA-ABS (serum and CSF) PCR	Thin motile corkscrew bacterium on dark field microscopy	Genitourinary, hematologic dissemination	Meningitis, myelopathy, neuropsychiatric	Normal, meningeal enhancement, myelitis, brain atrophy	Genital lesions, cutaneous

Abbreviations: AFB, acid-fast bacillus; CNS, central nervous system; CSF, cerebrospinal fluid; FTA-ABS, fluorescent treponemal antibody absorption; PCR, polymerase chain reaction; VDRL, venereal disease research laboratory; WBC, white blood count.

impaired cell-mediated immunity, especially HIV infection, people with hematologic malignancies, solid-organ transplant recipients, and patients on chronic corticosteroids or other immunosuppressive therapy. In patients infected with HIV, cryptococcal meningitis is the most common systemic fungal infection and a frequent etiology of CNS infection.²

The clinical manifestations of infection with *C neoformans* depend largely on the host immune status. Severity of infection varies from asymptomatic incidental pulmonary nodules to widely disseminated disease. Patients with HIV and CD4+ cell counts of less than 50 cells/ μ L are especially vulnerable to disseminated infection and meningitis.³ Immunosuppressed patients with cryptococcal meningitis frequently present with indolent nonspecific symptoms and in some cases with isolated neurologic manifestations. In general, over 75% of patients present with headache and fever, which typically develop insidiously over 2 to 4 weeks.⁴ Nausea, vomiting, and altered mental status occur in about half of the patients. Signs and symptoms of meningismus affect less than 25% of patients. Visual symptoms, such as diplopia and blindness, occur in about 20% of patients, most often in immunocompetent patients. Seizures and focal neurologic deficits occur in 10% of patients and are generally caused by space-occupying lesions such as cryptococcomas or granulomas. Two of the most dangerous complications of cryptococcal meningitis are elevated ICP and hydrocephalus.^{5,6}

The diagnosis of cryptococcal meningitis should be considered in patients presenting with a subacute presentation of headache and fever, especially in the setting of HIV infection or immunosuppression. Computerized tomography and MRI are nonspecific for the diagnosis of cryptococcal meningitis but may reveal hydrocephalus, cerebral edema, leptomeningeal enhancement, or cryptococcomas (Figure 2). Lumbar puncture, the diagnostic procedure of choice, is often notable for increased opening pressure, a mild mononuclear pleocytosis, increased protein, and low glucose concentrations. The CSF cryptococcal capsular polysaccharide antigen (CRAg) assay is both sensitive and specific for cryptococcal meningitis and also provides a quantitative titer that is useful for prognostication.⁷ The CRAg is not useful for determining response to therapy. Because the cryptococcal antigen (CRAg) lateral flow assay has nearly 100% sensitivity and specificity on CSF samples, it is considered for point-of-care diagnosis of cryptococcal meningitis.⁸ Fungal culture for the organism is 90% sensitive and can also be useful for speciation.

A combination of antifungal medication and aggressive treatment of hydrocephalus is integral to the successful treatment of patients with cryptococcal meningitis. Amphotericin B (AmB) plus flucytosine, as compared with AmB alone, is associated with improved survival of patients with cryptococcal meningitis.⁹ Hydrocephalus causing elevated ICP can be managed through a variety of treatments. Patients with elevated ICP should undergo daily lumbar punctures to reduce opening pressure until normal opening pressure is maintained consistently; some patients may require multiple daily lumbar

Figure 2. Magnetic resonance imaging of the brain of cryptococcal meningitis. A, B, and D, Magnetic resonance imaging T1 postcontrast imaging shows avid leptomeningeal enhancement from fungal meningitis. C, Magnetic resonance imaging diffusion-weighted imaging (DWI) demonstrates cortical areas of restricted diffusion indicating acute ischemic strokes, likely secondary to inflammation and infarction of end arteries.

punctures. For those patients requiring frequent lumbar punctures, placement of a lumbar drain or a ventriculostomy can serve as a temporary measure to control ICP.^{10,11} A recent retrospective study suggests elevated ICP in patients with cryptococcal meningitis is associated with higher mortality and aggressive management of ICP during the initial 5 days was more important than initial antifungal management alone for survival.¹²

Aspergillus

Historically, disease from *A fumigatus* was limited to individuals with repetitive exposure to pathogens, producing a mild condition known as farmer's lung. *Aspergillus* subsp were also known to produce lung aspergillomas, characterized as an overgrowth of fungus in preexisting cavitory lung lesions. More recently, the incidence and severity of *Aspergillus* subsp infection have increased due to a growing number of people living with immunosuppression, leading to more cases of invasive aspergillosis. Populations significantly at risk of invasive aspergillosis include patients undergoing treatment for hematologic malignancies, recipients of allogeneic hematopoietic stem cell or solid-organ transplantation, people who are HIV infected, and individuals with chronic granulomatous disease.¹³

Figure 3. Magnetic resonance imaging of the brain of central nervous system aspergillosis. A, Magnetic resonance imaging T2 fluid attenuation inversion recovery (FLAIR) image demonstrates diffuse leptomeningeal hyperintensity with parenchymal involvement of the bilateral frontal and parietal lobes. B-D, Magnetic resonance imaging diffusion-weighted imaging (DWI) sequence shows multiple areas of restricted diffusion indicating acute ischemic infarctions caused by angioinvasion of the organism.

Cerebral aspergillosis occurs in approximately 10% to 20% of patients with invasive disease and results from hematogenous dissemination of the organism or direct extension from rhinosinusitis.¹⁴ Central nervous system infection can present as a solitary mass lesion, cavernous sinus thrombosis, multiple intracranial abscesses, acute or chronic basilar meningitis, vasculitis, or myelitis.¹⁵ Pathologically, cerebral aspergillosis has a propensity for vascular invasion, infarction, hemorrhage, and aneurysm formation; as a result, the clinical presentation may mimic cerebral vasculitis, ischemic or hemorrhagic infarction, or subarachnoid hemorrhage (Figure 3). In patients with suspected cerebral aspergillosis, it is important to examine the lungs and sinuses for evidence of infection and potential sites for obtaining biopsy or culture material. Neuroimaging can be helpful in the evaluation of cerebral aspergillosis. Magnetic resonance imaging of the brain may demonstrate dural enhancement adjacent to infected paranasal sinuses, indicating direct extension of infection.¹⁶

Several serum laboratory markers can aid in the diagnosis of invasive aspergillosis. Enzyme-linked immunosorbent assay (ELISA) testing for the fungal cell wall constituents galactomannan and β -D-glucan should be considered. The CSF galactomannan assay using latex agglutination or ELISA

may be useful adjunct to serum testing; however, data are limited to small sample sizes with variable performance and reliability (sensitivity of 70%-90%).¹⁷ Several polymerase chain reaction (PCR) assays can detect *Aspergillus* subsp in blood and bronchoalveolar lavage (BAL) fluid samples; a recent study to detect *Aspergillus* subsp in fresh tissue and BAL fluid reported a sensitivity and specificity values of 86% and 100%.¹⁸ Experience with PCR to detect *Aspergillus* subsp in CSF samples is limited.

Unfortunately, cerebral aspergillosis, especially in an immunocompromised patient, is difficult to treat and has a high mortality rate. The use of voriconazole, a newer antifungal agent, has reduced the mortality of an infection that was previously associated with almost universal mortality. Clinical trials have demonstrated that voriconazole is more effective than AmB as initial therapy for invasive aspergillosis and is associated with significantly improved survival (71% vs 58%, respectively).¹⁹ In vitro studies evaluating combination therapy with voriconazole and caspofungin for *Aspergillus* subsp have provided promising results in patients with invasive aspergillosis.^{20,21}

Mycobacterium

Tuberculous meningitis is an aggressive form of extrapulmonary disease that is more common in patients coinfecting with HIV. Meningitis is typically preceded by nonspecific symptoms of malaise, anorexia, fatigue, weight loss, fever, myalgia, and headache. In immunocompetent patients, headache, vomiting, meningeal signs, focal deficits, vision loss, cranial nerve palsies, and raised ICP are characteristic clinical features. Cerebral vessels may be affected by adjacent meningeal inflammation, producing vasospasm, constriction, and eventually thrombosis with cerebral infarction.²² The hallmark pathologic feature of tuberculous meningitis is the presence of a thick exudate most prominent in the basilar meninges (Figure 4). This exudate can block the flow of CSF and result in hydrocephalus and multiple cranial neuropathies. Chest CT is sensitive for detecting pulmonary abnormalities in patients with tuberculous meningitis. Mediastinal and hilar lymphadenopathy, miliary pattern, and bronchopneumonic infiltrate are frequently noted.

Although CSF acid-fast bacillus (AFB) smear and culture are crucial for making a diagnosis of tuberculous meningitis, there is a wide range of reported sensitivities for AFB smear; sensitivities can reach as high as 52% with large volume of CSF samples (>6 mL), and microscopic examination for at least 30 minutes.²³ Conventional CSF culture for *M tuberculosis* on Lowenstein-Jensen medium is positive in approximately 45% to 90% of cases but usually takes several weeks for a positive result.²⁴ Characteristic CSF abnormalities include a mononuclear cell pleocytosis, low glucose concentration, and elevated protein concentration. The CSF pleocytosis can be lower in HIV-infected patients.²⁵ Of note, 16% of patients with confirmed *Cryptococcus*, 5% with TB,

Figure 4. Magnetic resonance imaging of the brain of tuberculosis meningitis. A and B, Magnetic resonance imaging T1 postcontrast imaging demonstrates diffuse leptomeningeal enhancement and hydrocephalus. C and D, Magnetic resonance imaging T1 postcontrast with discrete areas of parenchymal infiltration and the presence of tuberculomas located primarily in the deep gray matter. E-F, Magnetic resonance imaging T1 postcontrast imaging displays the predilection for the basilar meninges.

and 4% with bacterial meningitis will have normal CSF cell counts and biochemistry.²⁶ Detection of *M tuberculosis* DNA in CSF by PCR assay may be a useful ancillary diagnostic test, with a nearly 100% specificity but a sensitivity that varies between 30% and 50%, thus limiting its usefulness. The likelihood of detecting *M tuberculosis* is increased if repeat smear, culture, and PCR are performed on serial CSF samples.²⁷

Both CT and MRI of the brain are valuable for diagnosing tuberculous meningitis and evaluating complications. Characteristic abnormalities include enhancement of the basilar meninges, exudates, hydrocephalus, and periventricular infarcts. Empiric treatment should be initiated when tuberculous meningitis is initially suspected, as the organism grows slowly, speciation can take weeks, and earlier treatment is associated with better outcomes. First-line antituberculous medications include rifampicin, isoniazid, pyrazinamide, ethambutol, and streptomycin. Most first-line anti-TB drugs (except ethambutol) achieve satisfactory levels in the CSF.²² Adjunctive corticosteroids result in significantly reduced death and disabling residual neurologic deficits and should be used regardless of HIV status, although evidence for added benefit for HIV-infected patients is inconclusive.²⁸⁻³⁰

Syphilis

Although neurosyphilis can produce protean manifestations, this article will limit the discussion to syphilitic meningitis. Syphilitic meningitis typically presents in the secondary stage of syphilis, within 2 years of acquiring infection. Although less common than other forms of neurosyphilis, abnormal CSF with leukocytosis and elevated protein occur in up to 25% of patients.^{31,32} The most common presenting symptoms include headache, photophobia, nausea and vomiting, meningismus, and cranial nerve deficits. Although any cranial nerve can be affected, cranial nerves VII and VIII are most commonly affected.

In syphilitic meningitis, CSF typically has a mononuclear predominant pleocytosis (greater than 10 cells/2 L), elevated protein concentration (greater than 45 mg/dL), and normal or decreased glucose concentration. Although CSF immunologic tests, such as venereal disease research laboratory (VDRL), are usually abnormal in syphilitic meningitis (70%-80% sensitivity³³), a negative result does not rule out neurosyphilis. The CSF fluorescent treponemal antibody absorption testing is less specific but more sensitive than CSF-VDRL and may be used to exclude the diagnosis. More recently, PCR assays have been developed to detect *Treponema pallidum* in the CSF, but 50%

of patients with syphilitic involvement of the CNS have a negative PCR. Other new techniques include using CSF-fluorescent treponemal antibody and percentage of CSF-B cells when CSF-VDRL is negative to aid in establishing the diagnosis of neurosyphilis.³⁴

Penicillin is the first-line therapy for neurosyphilis. The Centers for Disease Control and Prevention recommends 18 million units to 24 million units of aqueous penicillin G per day administered as 3 million units to 4 million units intravenously (IV) every 4 hours or as continuous infusion for 10 to 14 days. An alternative is procaine penicillin 2.4 million units intramuscularly daily with probenecid 500 mg orally 4 times daily for 10 to 14 days.^{35,36}

Autoimmune Causes of Chronic Meningitis

Central nervous system involvement has been associated with nearly every autoimmune disease. Chronic meningitis is a presenting constellation of symptoms for a select group of diseases including sarcoidosis, lupus, Behçet disease, and vasculitis. Many patients with autoimmune disease are managed with immunosuppressant medications and are thus at increased risk of acquiring infectious meningitis. It is critical to carefully evaluate patients for potential infectious and neoplastic etiologies prior to administering immunosuppressive medications or steroids for the treatment of suspected autoimmune meningitis. If needed, serologic testing and brain biopsy should be obtained to confirm the diagnosis prior to empiric treatment.

Neurosarcoidosis

Sarcoidosis is a multisystem granulomatous disease affecting the CNS in up to 25% of patients. Although sarcoidosis has a predilection for the lungs, anterior uvea, lymphatic system, and skin, any organ, including the nervous system, can be affected. The most common clinical presentations of neurosarcoidosis include cranial neuropathies, seizures, meningitis, mass lesions, hypothalamic or pituitary involvement, and spinal cord lesions. Cranial neuropathies occur in 50% to 75% of patients and are most often the result of elevated ICP, granulomas, or basilar meningitis. The most common cranial neuropathy is unilateral or bilateral facial palsy, hearing loss, or optic neuropathy. Acute and chronic meningitis occur in up to 26% of patients with neurosarcoidosis.^{37,38}

Diagnosis of neurosarcoidosis is difficult and often requires a combination of medical history with neuroimaging, serologic and CSF data, and tissue biopsy. The diagnosis of systemic sarcoidosis is typically made through biopsy of lymph nodes, lung, liver, skin, or conjunctiva with histologic demonstration of noncaseating granulomas consisting of epithelioid cells and macrophages. Serum angiotensin-converting enzyme (ACE) level is elevated in 50% of patients with neurosarcoidosis.³⁸ Cerebrospinal fluid analysis typically reveals a lymphocytic pleocytosis (10-200 cells/2 L) with

significantly elevated protein concentration (2 g/L or greater) and low glucose concentration. The CSF abnormalities in neurosarcoidosis are most pronounced in patients with diffuse leptomeningeal enhancement on MRI.³⁹ Opening pressure is often elevated. The CSF oligoclonal bands may be present, most often in the setting of an elevated protein concentration. The CSF-ACE levels are nonspecific but can be elevated with neurosarcoidosis. Magnetic resonance imaging with gadolinium reveals leptomeningeal enhancement in up to 40% of patients with neurosarcoidosis, with the basilar meninges most often involved. Dural enhancement is present in up to 30% of cases. Intraparenchymal mass lesions or granulomas may be solitary or multiple and typically enhance with gadolinium. Brain biopsy is not routine but may be useful when meningeal or cerebral abnormalities are easily accessible. Enhancement or thickening of the pituitary or hypothalamic masses are present in 18% of patients with neurosarcoidosis. Although the facial nerve is the most common cranial neuropathy, on MRI, the optic nerve is most frequently abnormal, displaying enhancement and thickening.⁴⁰

Corticosteroids are the mainstay of treatment for neurosarcoidosis, with recommended initial doses of 40 to 60 mg/d, followed by a slow taper. Patients with severe symptoms may be treated with high-dose methylprednisolone (1 g IV for 3-5 days) followed by oral prednisone. Steroid-sparing immunosuppressive medications, including mycophenolate, azathioprine, methotrexate, cyclophosphamide, infliximab, and hydroxychloroquine, have been used with varying degrees of success; these medications are often used for long-term suppression.⁴¹

Systemic Lupus Erythematosus

Meningitis associated with SLE is typically associated with aseptic CSF. However, as many patients are treated with chronic immunosuppressive therapy, infectious meningitis should be considered in patients with SLE who have been treated with immunosuppressive therapy and develop fever, altered mental status, meningeal signs, and nausea or vomiting. Compared to SLE-associated aseptic meningitis, patients with infectious meningitis are typically older, develop mental status changes, and have plasma leukocytosis with neutrophilia, as well as a marked CSF pleocytosis and hypoglycorrhachia.⁴²

Common manifestations of SLE affecting the CNS include cerebrovascular disease (CVD) and seizures. Neuropsychiatric manifestations are relatively uncommon (1%-5%) but can produce severe cognitive dysfunction, major depression, acute confusional state (ACS), or psychosis. Risk factors for CNS involvement are previous or concurrent severe neuropsychiatric lupus (for cognitive dysfunction and seizures) and antiphospholipid antibodies (for CVD, seizures, and chorea).⁴³ No single diagnostic test is both sensitive and specific for CNS SLE. Assessment should include neurologic and rheumatologic evaluations, serologic testing of immune parameters, and

neuroimaging. Serum antibodies detected in patients with CNS-SLE include antinuclear antibody (82%), antidouble-stranded DNA (79%), antiribosomal P antibodies (61%), anticardiolipin immunoglobulin G (IgG; 15%), anti- β_2 glycoprotein IgG (65%), and anti-N-methyl-D-aspartate receptor (35%). Low serum complement (C3 and C4) and elevation of sedimentation rate may be supportive of disease; however, normal values do not exclude CNS SLE. These antibody titers do not typically change with treatment or with resolution of symptoms.^{44,45}

Primary Angiitis of the CNS

Primary angiitis of the CNS (PACNS) is characterized by inflammation and destruction of cerebral vessels without systemic involvement. Patients may present with a history of years of headache, encephalopathy, seizures, cognitive and behavioral changes, ataxia, recurrent TIAs, or focal neurologic deficits.⁴⁶ Symptoms of chronic meningitis can precede diagnosis by several years. Diagnostic criteria include the presence of acquired and unexplained neurologic or psychiatric deficits, presence of angiographic or histopathologic evidence of angiitis in the CNS, and no evidence of systemic or other disorders that may mimic the disease.

The combination of serologic studies, CSF analysis, angiography, MRI, and brain biopsy are essential for diagnosing PACNS. Biopsy is the gold standard for diagnosis but has low sensitivity. More importantly, biopsy is useful in identifying lesions that may mimic PACNS, such as infection or malignancy, which are found in up to 40% of patients.⁴⁷ Serum erythrocyte sedimentation rate and C-reactive protein are typically normal in PACNS and elevated in conditions that mimic PACNS. The CSF analysis is abnormal in over 90% of patients and usually demonstrates a modest lymphocytic pleocytosis (less than 20 cells/2 L), elevated protein concentration (median less than 120 mg/dL), and normal glucose concentration. The CSF examination is crucial for excluding infectious and neoplastic mimics of PACNS.

Cranial MRI may reveal infarction in up to half of the patients, and nonspecific subcortical white matter, deep white matter, and cortical T2-weighted hyperintensities are often present. Gadolinium enhancement of the leptomeninges occurs in 8% of patients. Cerebral angiography is commonly used to aid in the diagnosis of PACNS and classically demonstrates alternating areas of dilation and stenosis that can be smooth or irregular. These findings are nonspecific for PACNS and can be seen with other disorders, including infection, radiation, atherosclerosis, and vasospasm. Sensitivity of angiography varies from 40% to 90%. Although the diagnosis of PACNS can be difficult to confirm, patients with normal CSF, angiography, and MRI are extremely unlikely to have PACNS.⁴⁸

Treatment of PACNS includes immunosuppression with a combination of glucocorticosteroids and cyclophosphamide. High-dose oral prednisone (1 mg/kg/d) or IV pulse methylprednisolone for 3 days, followed by oral prednisone, is recommended. Cyclophosphamide, azathioprine, or mycophenolate

mofetil is most commonly used for long-term immunosuppression. Disease activity can be monitored with serial neurologic examinations and MRI scans.⁴⁶

Neoplastic Causes of Chronic Meningitis

Neoplastic involvement of the CNS should be considered in the differential diagnosis for patients presenting with signs and symptoms of chronic meningitis. Leptomeningeal carcinomatosis (LMC), or carcinomatous meningitis, is defined as malignant seeding or infiltration of the leptomeninges. Leptomeningeal carcinomatosis is most commonly associated with hematologic malignancies, but solid tumors and primary brain tumors can infiltrate the meninges in up to 5% of patients. Autopsy studies reveal that up to 19% of patients who have cancer with neurologic symptoms also have LMC.⁴⁹

Patients classically present with signs and symptoms of multifocal involvement of the neuraxis due to involvement of the cerebral hemispheres, brain stem, cranial nerves, spinal cord, or nerve roots. The most common presenting symptoms include headache, encephalopathy, nuchal rigidity, diplopia, weakness, and radicular pain. Cranial neuropathies may include trigeminal neuropathy, facial weakness, and hearing loss. Leptomeningeal carcinomatosis may precipitate obstructive hydrocephalus, and radionuclide scans reveal impaired CSF flow in 70% of patients with LMC.⁵⁰

Diagnosis of LMC is made by clinical examination, CSF analysis, and gadolinium-enhanced MRI. Lumbar puncture typically reveals elevated opening pressure, leukocytosis, and elevated protein and low glucose concentrations. The CSF cytology should be sent to evaluate for neoplastic cells. The sensitivity of a single, large volume CSF sample is 38% to 66%; if 3 large volume CSF samples are performed, the sensitivity increases to 90%.⁴⁹ Gadolinium-enhanced MRI is the imaging modality of choice and typically reveals contrast enhancement of the meninges, cortical convexities, basilar cistern, and cauda equina (Figure 5). Meningeal biopsy of contrast-enhancing lesions remains the gold standard for definitive diagnosis of LMC.

Idiopathic Chronic Meningitis

Despite a clinician's best effort, there remain a large number of patients who remain undiagnosed. A retrospective review of 49 patients with chronic idiopathic meningitis evaluated at Mayo Clinic identified an etiology in 10 patients, with 8 of the 10 having a neoplastic cause. Overall, 24% of brain biopsies in this population yielded a diagnosis. Of the 39 undiagnosed cases, 85% of patients had a good outcome despite a prolonged illness. Corticosteroid therapy was effective in 52% of the patients treated but did not influence the outcome.⁵¹ In those cases where history, examination, CSF analysis, novel testing, and biopsy fail to yield answers, clinicians may choose to offer empiric steroids.

Figure 5. Magnetic resonance imaging of the brain of leptomeningeal carcinomatosis. A, T2-weighted coronal magnetic resonance imaging (MRI) of the brain shows enlargement of the ventricular system consistent with hydrocephalus. Diffuse white matter abnormalities are due to a history of whole brain radiation. B, T1 with gadolinium shows diffuse nodular pachymeningeal enhancement with hydrocephalus. C and D, Magnetic resonance imaging images demonstrate temporal horn enlargement due to hydrocephalus. Leptomeningeal hyperintensities are apparent in (C) secondary to inflammation in the subarachnoid space.

Conclusion

Chronic meningitis is a common diagnostic dilemma for the neurohospitalist. Although most chronic meningitis can be divided into infectious, autoimmune, and neoplastic etiologies, idiopathic causes of chronic meningitis, such as chemical meningitis or syndrome of transient headache and neurologic deficits with CSF lymphocytosis, may present with similar symptoms and CSF pleocytosis. Early diagnosis and treatment remain crucial for neurologic recovery. Evaluation of suspected chronic meningitis should include a detailed history and physical examination as well as CSF diagnostics, serologic studies, and biopsy of brain or other abnormal tissue (eg, lymph node or lung), when indicated. Empiric treatment with antibiotics, antivirals, antifungals, and steroids should be implemented on a case-by-case basis.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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