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144 Chronic and Recurrent Meningitis

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Chronic and Recurrent Meningitis Chronic inflammation of the meninges (pia, arachnoid, and dura) can produce profound neurologic disability and may be fatal if not success fully treated. Chronic meningitis is diagnosed when a characteristic neurologic syndrome exists for >4 weeks and is associated with a per sistent inflammatory response in the cerebrospinal fluid (CSF) (white cell count >5/μL). The causes are varied, and appropriate treatment depends on identification of the etiology. Five categories of disease account for most cases of chronic meningitis: (1) meningeal infections, (2) malignancy, (3) autoimmune inflammatory disorders, (4) chemi cal meningitis, and (5) parameningeal infections. In addition, there is increasing recognition that some patients with recurrent meningitis may have monogenic autoinflammatory disorders. ■ ■CLINICAL PATHOPHYSIOLOGY Neurologic manifestations of chronic meningitis (Table 144-1) are determined by the anatomic location of the inflammation and its con sequences. Persistent headache, clinical signs of hydrocephalus, cranial neuropathies, radiculopathies, and cognitive or personality changes are the cardinal features. Meningeal signs are uncommon in chronic meningitis. These manifestations can occur alone or in combination. When they appear in combination, it may be indicative of widespread dissemination of the inflammatory process along CSF pathways. In some cases, the presence of an underlying systemic illness points to the probable cause of the meningitis (Fig. 144-1). The diagnosis of chronic meningitis is usually made when the clinical presentation prompts the physician to examine the CSF for signs of inflammation. CSF is produced by the choroid plexus of the cerebral ventricles, exits through the foramina in the fourth ventricle into the subarachnoid space surrounding the brain and spinal cord, circulates around the base of the brain and over the cerebral hemispheres, and is resorbed by arachnoid villi projecting into the superior sagittal sinus where it mixes with blood in the venous sinuses. Recently, a cerebral lymphatic system has been identified that drains the dura mater (Chap. 435); however, its role in chronic meningitis has not been studied. CSF flow provides a pathway for rapid spread of infectious and other infiltrative processes over the brain, spinal cord, cranial, and spinal nerve roots. Spread from the subarachnoid space into brain parenchyma may occur via the arachnoid cuffs that surround blood vessels that penetrate brain PART 5 Infectious Diseases TABLE 144-1 Symptoms and Signs of Chronic Meningitis SYMPTOM SIGN Chronic headache ± Papilledema Neck or back pain/stiffness Brudzinski’s or Kernig’s sign of meningeal irritation Change in personality Altered mental

status—drowsiness, inattention, disorientation, memory loss, frontal release signs (grasp, suck, snout), perseveration Facial weakness Peripheral seventh CN paresis Double vision Paresis of CNs III, IV, and/or VI Diminished vision Papilledema, CN II (optic atrophy/inflammation) Hearing loss Eighth CN paresis Arm or leg weakness Myelopathy or radiculopathy Numbness in arms or legs Myelopathy or radiculopathy Urinary retention/ incontinence Myelopathy or radiculopathy Frontal lobe dysfunction (hydrocephalus) Clumsiness Ataxia Abbreviation: CN, cranial nerve.

tissue (Virchow-Robin spaces). Microorganisms can travel along these perivascular spaces to enter the brain. Intracranial Meningitis In intracranial meningitis, nociceptive nerve fibers of the meninges are stimulated by the inflammatory pro cess, resulting in headache, neck pain, or back pain. Obstruction of CSF pathways at the cerebral aqueduct or arachnoid villi may produce hydrocephalus and signs and symptoms of raised intracranial pressure (ICP), including headache, vomiting, apathy or drowsiness, gait insta bility, papilledema, visual loss, impaired upgaze, or palsy of the sixth cranial nerve (CN VI). Cognitive and behavioral changes during the course of chronic meningitis may also result from vascular damage due to inflammation around the blood vessels in the subarachnoid space, causing infarction. Inflammatory deposits seeded via the CSF circula tion are often prominent around the brainstem and cranial nerves and along the undersurface of the frontal and temporal lobes. Such cases, termed basal meningitis, often present as multiple cranial neuropathies (Chap. 452), with some combination of decreased vision (CN II), facial weakness (CN VII), decreased hearing (CN VIII), diplopia (CNs III, IV, and VI), sensory or motor abnormalities of the oropharynx (CNs IX, X, and XII), decreased olfaction (CN I), or decreased facial sensa tion and masseter weakness (CN V). Involvement of the lower CNs is more common because the inflammatory exudate tends to collect at the base of the brain. Spinal Meningitis In spinal meningitis, injury may occur to motor and sensory nerve roots as they traverse the subarachnoid space and penetrate the meninges. These cases present as multiple radicu lopathies with combinations of radicular pain, sensory loss, motor weakness, and urinary or fecal incontinence. In some cases, chronic inflammation causes arachnoiditis with clumping of the lower nerve roots and thickening of the meninges. Preferential involvement of the lower nerve roots results from inflammatory cells that gravitate to the bottom of the intrathecal space. Meningeal inflammation can encircle and damage the spinal cord, resulting in a myelopathy. Slow progressive involvement of multiple CNs and/or spinal nerve roots is likely due to chronic meningitis. Electrophysiologic testing (electromy ography, nerve conduction studies, and evoked response testing) may be helpful in determining whether there is involvement of cranial and spinal nerve roots. Systemic Manifestations In some patients, evidence of systemic disease provides clues to the underlying cause of chronic meningitis. A complete history of travel, sexual exposure, insect bites, and other modes of exposure to infectious agents should be sought. Infectious causes are often associated with fever, malaise, anorexia, and signs of localized or disseminated infection outside the nervous system. Infec tious causes are of major concern in immunosuppressed patients and especially in patients with untreated HIV infection, in whom chronic meningitis is most often caused by Mycobacterium tuberculosis or Cryptococcus neoformans and may present without headache, fever, or meningeal signs. In this population, a high index of clinical suspicion needs to be maintained even when there is only mild confusion or a nonspecific headache syndrome even in the context of a pauicellular CSF profile. Noninfectious inflammatory disorders most often pro duce systemic manifestations first, but meningitis may be the initial manifestation. Carcinomatous meningitis, caused by CSF seeding with metastatic cancer cells, may or may not be accompanied by clinical evidence of the primary neoplasm. APPROACH TO THE PATIENT Chronic Meningitis The

occurrence of chronic or worsening headache, typically constant and nonfocal, clinical signs of hydrocephalus, cranial neuropathy, radiculopathy, and/or cognitive decline in a patient with or without fever should prompt consideration of a lumbar puncture for evidence of meningeal inflammation. On occasion, the diagnosis is made when a contrast-enhanced imaging study

Skin changes Behçet’s syndrome Systemic lupus erythematosus Cryptococcosis Blastomycosis Eyes Uveitis VKH syndrome Sarcoidosis Lymphoma Fungal infections Taenia solium Tuberculosis Herpes viruses Keratoconjunctivitis Sjögren’s syndrome Hypopyon Behçet’s syndrome Iridocyclitis Behçet’s syndrome Vasculitis Primary CNS vasculitis Bacterial, mycobacterial, spirochete, parasitic and viral infections Malignancy including lymphoma Paraneoplastic Rheumatoid arthritis ANCA associated vasculitis Sarcoidosis Sjögren’s syndrome Systemic lupus erythematosus Lymph nodes Lymphoma Metastatic adenocarcinoma Sarcoidosis Tuberculosis HIV Secondary syphilis Whipple’s disease Pancreas/GI tract IgG4-related disease Whipple’s disease Syphilis Sarcoidosis Bone/Bone marrow Lymphoma/Leukemia Fungal, bacterial and mycobacterial infections Brucellosis (vertebral osteomyelitis) Histiocytic disorders Metastatic adenocarcinoma Rheumatoid arthritis (joint space) FIGURE 144-1 Systemic manifestations that may provide clues to the etiology of chronic meningitis. (magnetic resonance imaging [MRI] or computed tomography [CT]) shows leakage of contrast agent into the meninges. Menin geal enhancement is always concerning with the exception of dural enhancement after lumbar puncture, neurosurgical procedures, concussion, or spontaneous CSF leakage. Once chronic meningitis is confirmed by CSF examination, effort is focused on identifying

Sarcoidosis Vasculitis CAPS (urticaria) Syphilis (diffuse rash including palms and soles) Lyme disease Sporotrichosis NOMID Trypanosomiasis IV drug use

Ear Fungal, mycobacterial, bacterial infections (chronic drainage) Varicella zoster virus Sinus Fungal and bacterial infections ANCA associated vasculitis IgG4-related disease Sarcoidosis Syphilis Mouth Dental abscess Behçet’s syndrome (aphthous ulcer) Herpes simplex virus types 1 and 2 HIV (candidiasis) Syphilis Whipple’s disease (oculomasticatory myorhythmia) CHAPTER 144 Thyroid IgG4-related diseases Chronic and Recurrent Meningitis Heart/Lungs Infectious source (right-to-left shunt, pneumonia) Sarcoidosis Syphilis Systemic lupus erythematosus IV drug use (endocarditis) Liver/Spleen Lymphoma Metastatic adenocarcinoma Sarcoidosis Tuberculosis Parasitic infection Brucellosis Rickettsial infection Genitals Herpes simplex virus Syphilis Behçet’s syndrome (aphthous ulcer) the cause (Tables 144-2 and 144-3) by (1) further analysis of the CSF, (2) diagnosis of an underlying systemic infection or noninfec tious inflammatory condition, or (3) pathologic examination of meningeal biopsy specimens. Two clinical forms of chronic meningitis exist. In the first, the symptoms are chronic and persistent, whereas in the second, there

TABLE 144-2 Infectious Causes of Chronic Meningitis CAUSATIVE AGENT CSF FORMULA HELPFUL DIAGNOSTIC TESTS RISK FACTORS AND SYSTEMIC MANIFESTATIONS Common Bacterial Causes Partially treated suppurative meningitis Mononuclear or mixed mononuclearpolymorphonuclear cells CSF culture and Gram’s stain; CSF 16s rRNA PCR Parameningeal infection Mononuclear or mixed mononuclearpolymorphonuclear cells Contrast-enhanced CT or MRI to detect parenchymal, subdural, epidural, or sinus infection Mycobacterium tuberculosis Mononuclear cells except polymorphonuclear cells in early infection (commonly

<500 WBC/μL); low CSF glucose; high protein Tuberculin skin test may be negative; interferon gamma release assay; PCR and AFB culture of CSF (sputum, urine, gastric contents if indicated); identify tubercle bacillus on acid-fast stain of CSF or protein pellicle Lyme disease (Bannwarth's syndrome) Borrelia burgdorferi Mononuclear cells; elevated protein Serum Lyme antibody titer; western blot confirmation; (patients with syphilis may have false-positive Lyme titer) Syphilis (secondary, tertiary) Treponema pallidum Mononuclear cells; elevated protein CSF VDRL; serum VDRL (or RPR); fluorescent treponemal antibodyabsorbed (FTA) or MHA-TP; serum VDRL and RPR may be negative in tertiary syphilis due to waning antibody levels or earlier in the disease course due to very elevated antibody levels (prozone effect) Uncommon Bacterial Causes Actinomyces Polymorphonuclear cells Anaerobic culture Parameningeal abscess or sinus tract (oral or dental focus); pneumonitis PART 5 Infectious Diseases Nocardia Polymorphonuclear; occasionally mononuclear cells; often low glucose Isolation may require weeks; weakly acid fast Brucella Mononuclear cells (rarely polymorphonuclear); elevated protein; often low glucose CSF antibody detection; serum antibody detection Whipple's disease Tropheryma whipplei Mononuclear cells Biopsy of small bowel or lymph node; CSF PCR for T. whipplei; brain and meningeal biopsy (with PAS stain and EM examination) Rare Bacterial Causes Leptospirosis (occasionally if left untreated may last 3–4 weeks) Fungal Causes Cryptococcus neoformans and var. gattii Mononuclear cells; count not elevated in some patients with AIDS India ink or fungal wet mount of CSF (budding yeast); blood and urine cultures; antigen detection in CSF (false negatives can occur in the setting of high antigen titers [prozone effect]) Coccidioides immitis Mononuclear cells (sometimes 10–20% eosinophils); often low glucose Antibody detection in CSF and serum, antigen detection in CSF Candida species Polymorphonuclear or mononuclear Fungal stain and culture of CSF IV drug abuse; postsurgery; prolonged IV therapy; disseminated candidiasis, recent epidural injection Histoplasma capsulatum Mononuclear cells; low glucose Fungal stain and culture of large volumes of CSF; antigen detection in CSF, serum, and urine; antibody detection in serum, CSF Blastomyces dermatitidis Mononuclear or polymorphonuclear Fungal stain and culture of CSF; biopsy and culture of skin, lung lesions; antibody detection in serum Aspergillus species Mononuclear or polymorphonuclear CSF culture Sinusitis; granulocytopenia or immunosuppression Sporothrix schenckii Mononuclear cells Antibody detection in CSF and serum; CSF culture Rare Fungal Causes Xylohypha (formerly Cladosporium) trichoides and other dark-walled (dematiaceous) fungi such as Curvularia; Drechslera; Mucor; and, after water aspiration, Pseudallescheria boydii; iatrogenic Exserohilum rostratum infection following spinal blocks and Fusarium solani following epidural anesthesia in two clinics in Durango, Mexico, during 2022–2023

History consistent with acute bacterial meningitis and incomplete treatment Otitis media, pleuropulmonary infection, right-to-left cardiopulmonary shunt for brain abscess; focal neurologic signs; neck, back, ear, or sinus tenderness Exposure history; previous tuberculous illness; immunosuppressed, anti-TNF therapy or AIDS; young children; fever, meningismus, night sweats, miliary TB on x-ray or liver biopsy; stroke due to arteritis History of tick bite or appropriate exposure history; erythema chronicum migrans skin rash; arthritis, radiculopathy, Bell's palsy and other cranial neuropathies, meningoencephalitis–multiple sclerosis-like syndrome Appropriate exposure history; HIV-seropositive individuals at increased risk of aggressive infection; fever; lymphadenopathy; generalized, nonpruritic, mucocutaneous rash; "dementia"; cerebral infarction due to endarteritis; myelopathy Associated brain abscess may be present Intake of unpasteurized dairy products; exposure to goats, sheep, cows; fever, arthralgia, myalgia, vertebral osteomyelitis Diarrhea, weight loss, arthralgias, fever; dementia, ataxia, paresis, ophthalmoplegia,

oculomasticatory myoclonus AIDS and immune suppression; pigeon exposure for C. neoformans, decaying wood exposure for C. var. gattii; skin and other organ involvement due to disseminated infection Exposure history—southwestern United States Exposure history—Ohio and central Mississippi River Valley; AIDS; mucosal lesions Midwestern and southeastern United States; usually systemic infection; abscesses, draining sinus, ulcers Traumatic inoculation; IV drug use; ulcerated skin lesion (Continued)

TABLE 144-2 Infectious Causes of Chronic Meningitis (Continued) CAUSATIVE AGENT CSF FORMULA HELPFUL DIAGNOSTIC TESTS RISK FACTORS AND SYSTEMIC MANIFESTATIONS Protozoal Causes Toxoplasma gondii Mononuclear cells Biopsy or response to empirical therapy in clinically appropriate context (including presence of antibody in serum) Trypanosomiasis Trypanosoma gambiense, T. rhodesiense Mononuclear cells; elevated protein Elevated CSF IgM; identification of trypanosomes in CSF and blood smear Rare Protozoal Causes Acanthamoeba sp. causing granulomatous amebic encephalitis and meningoencephalitis in immunocompromised and debilitated individuals; Balamuthia mandrillaris causing chronic meningoencephalitis in immunocompetent hosts Helminthic Causes Cysticercosis (infection with cysts of Taenia solium) Mononuclear cells; may have eosinophils; glucose level may be low Indirect hemagglutination assay in CSF; Serum serology with enzyme-linked immunoelectrotransfer blot preferred over crude extract ELISA; antigen or PCR testing in CSF Gnathostoma spinigerum Eosinophils, mononuclear cells Peripheral eosinophilia History of eating raw fish; common in Thailand and Japan; ocular involvement; subarachnoid hemorrhage; painful radiculopathy Angiostrongylus cantonensis Eosinophils, mononuclear cells Recovery of worms from CSF History of eating raw shellfish; common in tropical Pacific regions; often benign; ocular involvement (rare) Baylisascaris procyonis (raccoon ascarid) Eosinophils, mononuclear cells Immunoblot in CSF (Centers for Disease Control and Prevention) Rare Helminthic Causes Trichinella spiralis (trichinosis); Fasciola hepatica (liver fluke), Echinococcus cysts; Schistosoma spp. The former may produce a lymphocytic pleocytosis, whereas the latter two may produce an eosinophilic response in CSF associated with cerebral cysts (Echinococcus) or granulomatous lesions of brain or spinal cord. Viral Causes Mumps Mononuclear cells Antibody in serum No prior mumps or immunization; orchitis; may produce meningoencephalitis; may persist for 3–4 weeks Lymphocytic choriomeningitis Mononuclear cells; may have low glucose Antibody in serum; PCR for LCMV in CSF Contact with rodents or their excreta; may persist for

3–4 weeks Enteroviruses Mononuclear cells; may have low glucose Virus isolation and/or PCR for enteroviruses from CSF HIV (acute retroviral syndrome) Mononuclear cells PCR for HIV in blood and CSF HIV risk factors; rash, fever, lymphadenopathy; lymphopenia in peripheral blood; syndrome may persist long enough to be considered as “chronic meningitis”; or chronic meningitis may develop in later stages (AIDS) due to HIV Human herpes viruses Mononuclear cells PCR for HSV, EBV, CMV DNA; CSF antibody for HSV, EBV Abbreviations: AFB, acid-fast bacillus; CMV, cytomegalovirus; CSF, cerebrospinal fluid; CT, computed tomography; EBV, Epstein-Barr virus; ELISA, enzyme-linked immunosorbent assay; EM, electron microscopy; FTA, fluorescent treponemal antibody absorption test; HSV, herpes simplex virus; LCMV, lymphocytic choriomeningitis virus; MHA-TP, microhemagglutination assay–T. pallidum; MRI, magnetic resonance imaging; PAS, periodic acid–Schiff; PCR, polymerase chain reaction; RPR, rapid plasma reagin test; TB, tuberculosis; VDRL, Venereal Disease Research Laboratory test. are recurrent discrete episodes of illness. In the latter group, all symptoms, signs, and CSF parameters of meningeal inflammation

resolve completely between episodes either spontaneously or in response to a specific therapy. In such patients, the likely etiologies include Mollaret's meningitis, which is most often due to herpes simplex virus (HSV) type 2; chemical meningitis due to episodic leakage from an epidermoid tumor, craniopharyngioma, or choles teatoma into CSF; primary autoimmune inflammatory conditions, including Vogt-Koyanagi-Harada syndrome, Behçet's syndrome, systemic lupus erythematosus (SLE), rheumatoid arthritis, neu rosarcoidosis, IgG4-related disease, granulomatosis with polyan giitis, and primary central nervous system (CNS) vasculitis; and drug hypersensitivity with repeated administration of the offending agent. With the wider availability of whole genome sequencing, there is also a growing recognition that patients with inherited auto inflammatory syndromes like tumor necrosis factor (TNF) recep tor–associated periodic syndrome (TRAPS), cryoporin-associated periodic fever syndrome (CAPS), complement factor I deficiency,

Usually with intracerebral abscesses; common in

HIV-seropositive patients; fever Endemic in Africa; chancre, lymphadenopathy; prominent sleep disorder Usually with multiple cysts in basal meninges and hydrocephalus; cerebral cysts, ocular involvement; muscle calcification Infection follows accidental ingestion of B. procyonis eggs from raccoon feces; ocular involvement; fatal meningoencephalitis CHAPTER 144 Chronic and Recurrent Meningitis Congenital hypogammaglobulinemia; history of recurrent meningitis Recurrent meningitis due to HSV-2 (rarely HSV-1) often associated with genital recurrences; EBV associated with myeloradiculopathy, CMV with polyradiculopathy and neonatal-onset multisystem inflammatory disorder can have recurrent meningitis. The epidemiologic history is of considerable importance in diagnosis of chronic meningitis and may provide direction for selection of laboratory studies. Pertinent features include a history of tuberculosis or exposure; past travel to areas endemic for fungal infections (the San Joaquin Valley in California and southwestern states for coccidioidomycosis, midwestern states for histoplasmosis, southeastern states for blastomycosis); travel to the Mediterranean region or ingestion of imported unpasteurized dairy products (Brucella); time spent in wooded areas endemic for Lyme dis ease; exposure to sexually transmitted disease (syphilis, HSV-2); exposure of an immunocompromised host to pigeons and their droppings (Cryptococcus neoformans); exposure to decaying wood (Cryptococcus gattii); gardening (Sporothrix schenckii); ingestion of poorly cooked meat or contact with a household cat (Toxoplasma gondii); residence in Thailand or Japan (Gnathostoma spinigerum), Latin America (Paracoccidioides brasiliensis), or the South Pacific

TABLE 144-3 Noninfectious Causes of Chronic Meningitis CAUSATIVE AGENTS CSF FORMULA HELPFUL DIAGNOSTIC TESTS RISK FACTORS AND SYSTEMIC MANIFESTATIONS Malignancy Mononuclear cells; elevated protein; low glucose Repeated cytologic examination of large volumes of CSF; CSF exam by polarizing microscopy; clonal lymphocyte markers; deposits on nerve roots or meninges seen on myelogram or contrast-enhanced MRI; meningeal biopsy Chemical compounds (may cause recurrent meningitis) Mononuclear or PMNs; low glucose, elevated protein; xanthochromia from subarachnoid hemorrhage in week prior to presentation with "meningitis" Contrast-enhanced CT scan or MRI; cerebral angiogram to detect aneurysm. Enhancement and clumping of nerve roots of the cauda equina in arachnoiditis/ pachymeningitis Primary Inflammation CNS sarcoidosis Mononuclear cells; elevated protein; often low glucose Serum and CSF angiotensin-converting enzyme levels (insensitive); biopsy of extraneural affected tissues or brain lesion/meningeal biopsy, nodular meningeal and parenchymal enhancement Vogt-Koyanagi-

Harada syndrome (recurrent meningitis) Mononuclear cells Recurrent meningoencephalitis with uveitis, retinal detachment, alopecia, lightening of eyebrows and lashes, dysacousia, cataracts, glaucoma Isolated granulomatous angiitis of the nervous system Mononuclear cells; elevated protein Angiography (often normal with small vessel angiitis); meningeal biopsy may be necessary if confined to small vessels. VZV PCR in blood, CSF, and biopsy tissue; microhemorrhages with amyloid beta– related angiitis Systemic lupus erythematosus Mononuclear or PMNs Anti-dsDNA antibody, antinuclear antibodies PART 5 Infectious Diseases Behçet's syndrome (recurrent meningitis) Mononuclear or PMNs; elevated protein Rhombencephalitis Oral and genital aphthous ulcers; iridocyclitis; retinal hemorrhages; pathergic lesions at site of skin puncture Chronic benign lymphocytic meningitis Mononuclear cells Recovery in 2–6 months, diagnosis by exclusion Mollaret's meningitis (recurrent meningitis) Large endothelial cells and PMNs in first hours, followed by mononuclear cells PCR for HSV; MRI/CT to rule out epidermoid tumor or dural cyst Drug hypersensitivity PMNs; occasionally mononuclear cells or eosinophils Complete blood count (eosinophilia) Exposure to nonsteroidal anti-inflammatory agents, sulfonamides, isoniazid, tolmetin, ciprofloxacin, penicillin, carbamazepine, lamotrigine, IV immunoglobulin, OKT3 antibodies, phenazopyridine; improvement after discontinuation of drug; recurrence with repeat exposure Granulomatosis with polyangiitis (Wegener's) Mononuclear cells Chest and sinus radiographs; urinalysis; ANCA antibodies in serum; pachymeningitis on contrast-enhanced MRI Neonatal-onset multisystem inflammatory disorder Mononuclear and PMNs Gain-of-function mutation in NLRP3 gene leading to elevated IL-1β IgG4-related hypertrophic pachymeningitis Mild lymphocytic pleocytosis in some cases; normal to mildly increased protein; normal glucose Serum IgG4 levels frequently elevated; ESR and C-reactive protein; pachymeningitis on contrast-enhanced MRI; meningeal biopsy shows swirling "storiform" fibrosis with lymphocytic infiltrates, obliterative phlebitis and IgG4+ plasma cells TNF receptor–associated periodic fever syndrome (TRAPS) Mononuclear cells Mutation in TNFRSF1A gene leading to elevated TNF Complement factor I deficiency PMNs Mutation in complement factor I gene leading to low serum levels of factor I (or dysfunctional factor I) and C3 Cryoporin-associated periodic fever syndrome (CAPS) Mononuclear cells Heterozygous gain-of-function mutations within the NLRP3 gene Other: multiple sclerosis, Sjögren's syndrome, and rarer forms of vasculitis (e.g., Cogan's syndrome) Abbreviations: ANCA, antineutrophil cytoplasmic antibodies; CN, cranial nerve; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; HSV, herpes simplex virus; ICP, intracranial pressure; IL, interleukin; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PMNs, polymorphonuclear cells; TNF, tumor necrosis factor; VZV, varicella-zoster virus.

Metastatic cancer of breast, lung, stomach, or pancreas; melanoma, lymphoma, leukemia; meningeal gliomatosis; sarcoma; cerebral dysgerminoma History of recent injection into the subarachnoid space; history of sudden onset of headache; recent resection of acoustic neuroma or craniopharyngioma; epidermoid tumor of brain or spine, sometimes with dermoid sinus tract; pituitary apoplexy CN palsy, especially CN VII and CN II, including optic chiasm; hypothalamic dysfunction, especially diabetes insipidus; abnormal chest radiograph; peripheral neuropathy or myopathy; longitudinally extensive transverse myelitis Subacute dementia; multiple cerebral infarctions; recent zoster ophthalmicus Encephalopathy; seizures; stroke; transverse myelopathy; rash; arthritis; thromboembolism; renal and/ or pulmonary complications Recurrent meningitis; exclude HSV-2; rare cases due to HSV-1; occasional case associated with dural cyst Associated sinus, pulmonary, or renal lesions; CN palsies; skin lesions; peripheral neuropathy Recurrent fever, urticaria, arthralgia, sensorineural hearing loss, papilledema, increased ICP Headache; seizures;

focal symptoms from dural involvement in spinal cord/nerve roots, clivus, periorbital, vestibular, and brainstem structures. Systemic IgG4-related disease can involve many tissues including pancreas, thyroid, lungs, retroperitoneum, lacrimal, parotid and submandibular glands, orbits, kidney, aorta, liver Headache, seizures, tinnitus, skin rash, abdominal pain, lymphadenopathy, periorbital edema, joint pain, myalgia Recurrent, steroid-responsive, aseptic, neutrophilic meningitis with or without encephalitis; increased risk for systemic infections with encapsulated bacteria, glomerulonephritis, systemic lupus erythematosus and leukocytoclastic vasculitis Fever, urticaria, amyloidosis, arthralgia, sensorineural hearing loss, myalgias, papilledema, vision changes

(Angiostrongylus cantonensis); rural residence and raccoon expo sure (Baylisascaris procyonis); and residence in Latin America, the Philippines, sub-Saharan Africa, or Southeast Asia (Taenia solium/ cysticercosis, schistosomiasis). CNS meliodosis caused by Burkholderia pseudomallei is endemic in South Asia and Australia. Individu als with agammaglobulinemia or those receiving B cell–depleting therapy may be susceptible to chronic enterovirus meningitis. Focal cerebral signs in a patient with chronic meningitis sug gest the possibility of a brain abscess, parameningeal infection, or infarct; identification of a potential source of infection (chronic draining ear, sinusitis, dental abscess, right-to-left cardiac or pulmonary shunt, chronic pleuropulmonary infection) supports this diagnosis. In some cases, diagnosis may be established by recognition and biopsy of unusual skin lesions (Behçet’s syn drome, SLE, cryptococcosis, blastomycosis, Lyme disease, spo rotrichosis, trypanosomiasis, IV drug use) or enlarged lymph nodes (lymphoma, sarcoid, tuberculosis, HIV, secondary syphilis, or Whipple’s disease). Ophthalmologic examination may reveal uveitis (Vogt-Koyanagi-Harada syndrome, sarcoidosis, or CNS lymphoma), keratoconjunctivitis sicca (Sjögren’s syndrome), or iridocyclitis (Behçet’s syndrome) and is essential to assess visual loss from papilledema. M. tuberculosis can cause a wide spectrum of ophthalmologic pathology. If neurocysticercosis is suspected, it is important to rule out an intraocular infection requiring surgi cal treatment before initiating antihelminthic therapy. Aphthous oral lesions, genital ulcers, and hypopyon (inflammatory cells in the anterior chamber of the eye) suggest Behçet’s syndrome. Hepatosplenomegaly suggests lymphoma, sarcoid, tuberculosis, or brucellosis. Arthralgias could be indicative of Lyme disease or Whipple’s disease. The latter can also cause gastrointestinal symp toms, including diarrhea and abdominal pain. Herpetic lesions in the genital area or on the thighs suggest HSV-2 infection. A breast nodule; a suspicious hyperpigmented skin lesion; focal bone pain; hard, fixed lymph nodes; or an abdominal mass suggests possible carcinomatous meningitis. IMAGING Once the clinical syndrome is recognized as a potential mani festation of chronic meningitis, proper analysis of the CSF is essential. However, if the possibility of raised ICP exists, a brain imaging study should be performed before lumbar puncture. If ICP is elevated because of a mass lesion, brain swelling, or a block in ventricular CSF outflow (obstructive hydrocephalus), then lumbar puncture carries the potential risk of brain herniation. Obstruc tive hydrocephalus usually requires direct ventricular drainage. In patients with open CSF flow pathways, elevated ICP can still occur due to impaired resorption of CSF by arachnoid villi. In such patients, lumbar puncture is usually safe and may be therapeutic. Indeed, repetitive or continuous lumbar drainage may be necessary to prevent abrupt deterioration and death from raised ICP. In some patients, especially those with cryptococcal meningitis, fatal levels of raised ICP can occur without enlarged ventricles. Contrast-enhanced MRI or CT studies of the brain and spinal cord can identify meningeal enhancement, parameningeal infections (including brain abscess), encasement of the spinal cord (malignancy, inflammation, or infection), or nodular deposits on the meninges or nerve roots (malignancy, sarcoidosis, or

schistosomiasis) (Fig. 144-2). Imaging studies are also useful to guide biopsy of affected meninges. Lastly, a cyst that recurrently causes a chemical meningitis due to a leak may be better visualized in between clinical episodes when a recent leak has not shrunken the cyst volume. The patterns of enhancement of the different layers of the menin ges can be very informative and can be divided into two types: leptomeningeal (pia and arachnoid), when enhancement of the meninges follows the convolutions of the gyri and/or involves the meninges around the basal cisterns; and pachymeningeal (dura), when the enhancement is thick and linear or nodular along the inner surface of the calvarium, falx, or tentorium without extension

into the cortical gyri or basal cistern involvement. For example, infectious meningitis presents mostly as leptomeningitis, while lymphomatous meningitis can present as pachymeningitis. Angiographic studies can identify evidence of cerebral arteritis in patients with chronic meningitis and stroke. CEREBROSPINAL FLUID ANALYSIS The CSF pressure should be measured and samples sent for bacte rial, fungal, and mycobacterial culture; Venereal Disease Research Laboratory (VDRL) test; cell count and differential; Gram's stain; and measurement of glucose and protein. CSF VDRL is a highly specific, but not particularly sensitive, test for syphilis. If CSF VDRL is negative in an otherwise high-risk patient with positive treponemal antibodies in the serum and an otherwise unexplained CSF pleocytosis, empiric treatment for neurosyphilis may still be appropriate. Wet mount for fungus and parasites, India ink preparation, culture for fastidious bacteria and fungi, assays for cryptococcal antigen and oligoclonal immunoglobulin bands, and cytology should be performed. Other specific CSF tests (Tables 144-2 and 144-3) or blood tests and cultures should be ordered as indicated based on the history, physical examination, or prelimi nary CSF results (i.e., eosinophilic, mononuclear, or polymorpho nuclear meningitis). Rapid diagnosis may be facilitated by serologic tests and polymerase chain reaction (PCR) testing to identify DNA sequences in the CSF that are specific for the suspected pathogen. 16s ribosomal RNA (rRNA) PCR can be used to detect a broad range of bacterial causes of meningitis and can be particularly use ful in partially treated meningitis when the yield of culture is low. 18s and 28s rRNA PCR can similarly be useful for detecting a broad range of fungal species. In patients with suspected fungal infections, when other tests are negative, CSF assays for beta-glucans may be a useful adjunct in establishing the diagnosis. Building on progress in parallel deep sequencing and informatics, unbiased metagenomic next-generation sequencing is becoming generally available, repre senting an efficient and powerful method for diagnosis of challeng ing infectious cases. CHAPTER 144 Chronic and Recurrent Meningitis In most categories of chronic (not recurrent) meningitis, mononuclear cells predominate in the CSF. When neutrophils predominate after 3 weeks of illness, the principal etiologic considerations are Nocardia asteroides, Actinomyces israelii, Brucella, M. tuberculosis (5–10% of early cases only), various fungi (Blas tomyces dermatitidis, Candida spp., Histoplasma capsulatum, Aspergillus spp., Pseudallescheria boydii, Cladophialophora ban tiana), and noninfectious causes (SLE, exogenous chemical men ingitis). When eosinophils predominate or are present in limited numbers in a primarily mononuclear cell response in the CSF, the differential diagnosis includes parasitic diseases (A. canto nensis, G. spinigerum, B. procyonis, or Toxocara canis infection; cysticercosis; schistosomiasis; echinococcal disease; T. gondii infection), fungal infections (6–20% eosinophils along with a predominantly lymphocyte pleocytosis, particularly with coc cidioidal meningitis), neoplastic disease (lymphoma, leukemia, metastatic carcinoma), or other inflammatory processes (sar coidosis, hypereosinophilic syndrome). It is often necessary to broaden the number of diagnostic tests if the initial workup does not reveal the cause. In addition, repeated samples (three or more) of large volumes of lumbar CSF may be required to diagnose

certain infectious and malignant causes of chronic meningitis. Lymphomatous or carcinomatous meningitis may be diagnosed by examination of sections cut from a cell block formed by spinning down the sediment from a large volume of CSF. Flow cytometry for malignant cells may also be useful in patients with suspected carcinomatous meningitis. The diagnosis of fungal meningitis may also require large volumes of CSF for culture of sediment. If standard lumbar puncture is unrewarding, a cervical cisternal tap to sample CSF near to the basal meninges may be fruitful. Ventricular fluid may appear sterile in cases with active infection in the lower lumbar space.

A PART 5 Infectious Diseases C FIGURE 144-2 Chronic meningitis illustrating meningeal enhancement on contrast magnetic resonance imaging scan. A and B are images from a patient with chronic meningitis due to carcinoma. C and D are from a patient with chronic meningitis due to Cryptococcus infection. Arrows point to the most prominent areas of meningeal inflammation around the brainstem and cerebellar folia (A), cerebellum (C), along the dorsal spinal cord (B), and clumping of roots in the cauda equina (D). LABORATORY INVESTIGATION In addition to the CSF examination, an attempt should be made to uncover pertinent underlying illnesses. Tuberculin skin test, chest radiograph, urine analysis and culture, blood count and differential, renal and liver function tests, alkaline phosphatase, sedimentation rate, antinuclear antibody, anti-Ro antibody, anti-La antibody, rheu matoid factor, and IgG4 level are often indicated. In some cases, a thorough search for a systemic site of infection is indicated. Pul monary foci of infection may be present, particularly with fungal

B D or tuberculous disease. Hence, a CT or MRI of the chest and a sputum examination may be helpful. Abnormalities can be pursued by bronchoscopy or transthoracic needle biopsy. A tuberculin skin test is often placed, although the test has limited specificity and sensitivity for diagnosis of active disease. Where available, gamma interferon release assays may be used to diagnose latent tuber culosis. Liver, bone marrow, or lymph node biopsy may be diag nostic in some cases of miliary tuberculosis, disseminated fungal infection, sarcoidosis, or metastatic malignancy. Positron emission

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