Bacterial, Fungal, and Parasitic Infections of the Central Nervous System: Radiologic-Pathologic Correlation and Historical Perspectives

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Abbreviations: AIDS = acquired immunodeficiency syndrome, CNS = central nervous system, CSF = cerebrospinal fluid, DALY = disability-adjusted life year, FLAIR = fluid-attenuated inversion recovery, HIV = human immunodeficiency virus

RadioGraphics 2015; 35:1141–1169
Published online 10.1148/rg.2015140317
Content Code: NR

Introduction

In 1971, Abdul Omran proposed a theory of epidemiologic transition in developing countries that describes a long-term shift in mortality and disease patterns in these countries; he described three stages: “The Age of Pestilence and Famine,” “The Age of Receding Pandemics,” and “The Age of Degenerative and Man-Made Diseases” (1). The evolution from infectious to chronic diseases can be seen...
in annual mortality data published by the U.S. government that show that the mortality rate associated with infectious diseases has decreased dramatically during the 20th century, from 797 deaths per 100,000 persons in 1900 to 36 deaths per 100,000 persons in 1980 (2). The pattern is further substantiated by data from the World Health Organization on the global burden of disease in disability-adjusted life years (DALYs) that demonstrate an increasing prevalence of noncommunicable diseases (54% of worldwide DALYs in 2010, compared with 43% in 1990). In stark contrast, meningitis and encephalitis combined account for only 1.5% of DALYs (3). Nevertheless, infectious diseases continue to greatly affect the worldwide population, and with fairly easily accessible global travel, it is not unlikely that radiologists will encounter imaging manifestations of a disease more typical of “The Age of Pestilence and Famine” in a state-of-the-art radiology department in a part of the world now entrenched in “The Age of Degenerative and Man-Made Diseases.”

Familiarity with the wide range of infectious agents that can afflict the brain, spinal cord, and meninges remains an important aspect of neuroimaging. Despite many advances in medical technology and public health, global mortality rates associated with human immunodeficiency virus (HIV) infection, acquired immunodeficiency syndrome (AIDS), tuberculosis, and malaria have only recently begun to recede and these diseases remain a significant burden in certain regions of the world, particularly sub-Saharan Africa (4). In developed countries, advances in the treatment of autoimmune diseases and in organ transplantation have led to unintended but additional risk for infections that are more common in immuno-compromised patients and transplant recipients. Even in persons with normal immune surveillance, some extremely severe types of infection can lead to rapid death.

Communicable or infectious diseases are caused by microscopic organisms (bacteria, fungi, and protozoa), macroscopic organisms (worms), and microscopic particles (viruses and prions). The idea that microscopic “seeds” or “germs” could cause infections or epidemics was first proposed by Girolamo Fracastoro in 1546, more than a century before Anton van Leeuwenhoek used his advances in lensmaking to report the first observation of microscopic single-celled organisms in 1676. Nevertheless, a few more centuries would pass before Louis Pasteur proved that microorganisms are transmissible and ubiquitous agents that do not arise by spontaneous generation. This discovery was followed by Robert Koch’s work to establish one-to-one relationships between microorganisms and diseases, by successfully isolating the specific agents responsible for anthrax, tuberculosis, and cholera, then culminating with his four famous postulates in 1884 (5).

The discovery of microorganisms posed a challenge to the traditional two-kingdom classification system (established in 1735), which divided living things into Regnum Plantae or Regnum Animalia. Some of these unicellular lifeforms were neither plant-like (photosynthetic and nonmotile) nor animal-like (food ingesting and motile); therefore, a third kingdom of life, the Protista, was proposed in 1866. The advent of the electron microscope led to the discovery of single-celled organisms without a membrane-bound nucleus or organelles; these organisms were reclassified from Protista to a fourth kingdom, the Monera, in 1938 (6). On the basis of nutritional differences, a new kingdom, Fungi, was recognized as a unique form and separated from Plantae in 1969, thus completing the five-kingdom classification system of life that is the foundation of modern taxonomy (7). All of the kingdoms except Plantae (plants) include infectious organisms, which can be categorized as bacteria (Monera), fungi (Fungi), or parasites (both unicellular [Protista] and multicellular [Animalia]).

There are a wide range of neuroimaging findings in central nervous system (CNS) infections, often with considerable overlap, which makes determination of a specific diagnosis difficult. Correlation with laboratory tests, particularly cerebrospinal fluid (CSF) analysis, is considered to be essential in establishing a definitive diagnosis. With use of case reports from the archives of the American Institute for Radiologic Pathology, this article will explore the spectrum of bacterial,
fungal, and parasitic CNS infections, with recognition of microbiologic properties that may influence imaging appearances.

**Pyogenic Bacterial Infections**

Meningitis involves inflammation of the leptomeninges or pachymeninges covering the brain and spinal cord and may be caused by infectious or noninfectious agents. Descriptions of epidemic meningitis date back to 1805, although the causative bacterium *Neisseria meningitidis* was not identified until 1887. The introduction of lumbar puncture for CSF analysis by Heinrich Quincke in 1891 led to identification of two additional bacteria, *Streptococcus pneumoniae* and *Haemophilus influenzae*, which were responsible for nonepidemic cases of meningitis. All three bacteria colonize the nasopharynx and possess protective polysaccharide capsules, which served as antibody targets for anti-meningococcal serum therapy before the discovery of penicillin and more recently have been used for vaccine development against specific serotypes of *Haemophilus* species, meningococcus, and pneumococcus (8). Geographic spread from paranasal sinus, mastoid, or dental infection through valveless emissary veins, hematogenous spread in the context of extracranial infection, and direct inoculation through trauma or surgery may play a role in the development of meningitis (9). *N meningitidis*, *S pneumoniae*, and *H influenzae* are still the three main causes of acute pyogenic meningitis (not occurring during the neonatal period) in the 21st century. The annual incidence of bacterial meningitis in the United States from 2003 through 2007 was estimated to be 4100 cases (with 500 deaths); pneumococcus accounted for 58% of all cases, and group B *Streptococcus* species accounted for 86% of cases in patients less than 2 months of age (10).

Meningitis is a clinical and laboratory diagnosis. Less than half of patients with acute bacterial meningitis present with the classic triad of fever, neck stiffness, and altered mental status, although nearly 100% will have at least one of those symptoms (11). The presence of leukocytosis is variable. The mortality rate can reach as high as 30% (due to pneumococcus); therefore, blood cultures should be performed and empirical antibiotic therapy should be started immediately if meningitis is suspected, especially when symptoms include altered mental status or seizure (12). Vancomycin and a third-generation cephalosporin (such as cefotaxime or ceftriaxone) can be used to treat infection due to *Haemophilus* species, meningococcus, and penicillin-resistant pneumococcus. Adjunctive dexamethasone therapy may be administered to prevent neurologic complications. Risk factors such as defective cell-mediated immunity or recent neurosurgery are considered when determining additional antibiotic therapy requirements (13). Treatment of possible acute bacterial meningitis should not be delayed for performance of lumbar puncture or head computed tomography (CT), findings of which are likely to be normal in patients younger than 60 years of age who do not have a history of immunodeficiency, neurologic disease, recent seizure, altered mentation, or focal neurologic deficit (absence of these six risk factors has a negative predictive value of 97% for head CT findings [not meningitis]) (14). In a study involving 245 pediatric patients with bacterial meningitis, antibiotic pretreatment was found to have a relatively modest effect on the frequencies of positive CSF Gram stain results (62% of patients who received pretreatment, compared with 63% of patients who did not receive pretreatment), positive blood culture results (48% versus 66%), and positive CSF culture results (70% versus 88%) (15).

Cross-sectional imaging is neither sensitive nor specific for detection of meningitis. Sulcal effacement with slight hyperattenuation is typical on non–contrast material–enhanced CT images but may be subtle, accounting for frequent false-negative early CT findings. Abnormal hyperintensity may be visible in the cerebral sulci on T2-weighted fluid-attenuated inversion-recovery (FLAIR) magnetic resonance (MR) images as the result of increased protein content, but this finding is not specific for meningitis (Fig 1). Abnormal hyperintensity in the cerebral sulci on diffusion-weighted images (Fig 1c) is also not specific for meningitis; however, the finding is more consistent with pyogenic inflammation due to bacterial meningitis than with lymphocytic inflammation due to viral or aseptic meningitis. Abnormal enhancement of the pia and subarachnoid space (leptomeningeal) caused by inflammatory breakdown of the blood-brain barrier is seen in only 50% of patients (16). Thin linear enhancement in the cerebral sulci is the typical pattern seen in both acute pyogenic (bacterial) and lymphocytic (viral) meningitis, whereas thick nodular enhancement in the basal cisterns is more typical of granulomatous or carcinomatous meningitis (17). Additional MR imaging sequences that may be used for increased sensitivity for leptomeningeal disease include postcontrast T2-weighted FLAIR and delayed postcontrast T1-weighted sequences (18). Nevertheless, CSF analysis remains the reference standard for diagnosis of meningitis. Neuroimaging is most useful for excluding herniation before lumbar puncture and for detecting complications, such as hydrocephalus, venous thrombosis, or parenchymal or...
subdural infection, especially with *Streptococcus* or *Staphylococcus* species.

Cerebritis refers to pyogenic inflammation of the brain parenchyma and leads to abscess formation if untreated. During the 19th century, an intracranial abscess was essentially a death sentence until the development of aseptic surgery by Joseph Lister and cerebral localization by William Mac- 

ewen, one of the founders of modern neurosurgery (19). Macewen’s landmark monograph, *Pyogenic Infective Diseases of the Brain and Spinal Cord*, published in 1893 (2 years before the birth of diagnostic imaging), reported the successful surgical drainage of 18 intra-axial and five extra-axial ab- 
scesses, many resulting from chronic otomastoiditis. In 1926, Walter Dandy, a pioneer of early neurosurgery and neuroradiology (pneumoencephalography), reduced surgical morbidity by using needle rather than open drainage and by waiting 2 

weeks for encapsulation. The discovery of penicillin by Alexander Fleming in 1928 eventually led to the first antibiotic treatment of meningitis and cerebritis in 1943. Although intravenous antibiotic treatment penetrates brain abscesses to therapeutic levels, needle aspiration is still required in most cases for the best clinical outcome (20).

In 1983, Enzmann and Britt used the radiologic-pathologic correlation between serial postcontrast CT and surgery or autopsy findings to describe four stages of brain abscess development: early cerebritis, late cerebritis, early cap- 
sule, and late capsule (21,22). In early cerebritis, the neutrophilic response to the invasive organism manifests as ill-defined hypoattenuation with absent or variable enhancement on precontrast 

CT images. In late cerebritis, when the blood- 

brain barrier opens to allow fibroblast accumu-

lation at the margins, the postcontrast CT images show ringlike enhancement, which diff-

uses centrally on delayed images and suppresses after corticosteroid therapy. Fibroblasts initially 

create a reticulin matrix to block the necrotic material during early capsule formation, and the matrix later transitions to mature collagen over 2–4 weeks during late capsule formation. The development of the capsule is the signature imaging feature of an abscess. In both early and late 

abscess, the capsule manifests as a well-defined 

ring, which is hyperattenuated compared with central necrosis and peripheral edema on pre-

contrast CT images. Unlike in late cerebritis, in late abscess the ring enhancement reflects a well-

vascularized capsule and tends not to persist on delayed scans or suppress after administration of 

corticosteroid therapy. The capsule wall is often thinner medially because of the relatively poor 

vascuarity and reduced fibroblast migration, and the thin wall may predispose to daughter ab-

scesses or intraventricular rupture if located adja-

cent to the ventricular margin (21,22).

MR imaging findings parallel CT findings 

across the four stages of cerebritis and abscess 

(Figs 2, 3). Hyperintensity on T1-weighted im-

ages and hypointensity on T2-weighted images in the abscess capsule have been attributed to the paramagnetic effects of bactericidal free radicals generated by active macrophages (23). Suscep-

tibility-weighted imaging has confirmed these paramagnetic effects by measuring phase values 

in the abscess capsule (24).
Figure 2. Cerebritis. (a) Axial T2-weighted FLAIR MR image shows a thin region of hyperintensity along the right subinsular margin, bilateral posterior temporal lobes, and paramedian left frontal lobe (arrowheads). (b) Axial diffusion-weighted MR image reveals corresponding hyperintensity. (c) Axial contrast-enhanced T1-weighted MR image shows small areas of associated patchy enhancement (arrowheads).

When *Staphylococcus, Streptococcus, Haemophilus, Neisseria*, or gram-negative bacteria penetrate the epithelial barriers, polymorphonuclear leukocytes in the form of neutrophils are dispatched by the immune system to engulf and destroy the foreign invaders. Phagocytosis induces apoptosis in these short-lived first responders, and this process helps to control the acute inflammatory response (25). Pus is the viscous residuum of this battlefield strewn with fragmented remnants of bacteria and neutrophils to be cleared by another leukocyte, the macrophage. The high concentration of cellular debris in pyogenic infection has been correlated with restricted diffusion (Fig 3b and 3c) (26). Accordingly, diffusion-weighted MR imaging is regarded as the best sequence for differentiation of ring-enhancing pyogenic abscess from necrotic tumor (27). Although tumors or demyelinating lesions may show restricted diffusion, it is typically seen in the periphery and is related to high cellular density in that region. However, metastases, hematomas, or any ring-enhancing lesions with highly proteaseaceous or viscous contents may, on occasion, show central restricted diffusion; therefore, this finding is not pathognomonic for abscess (28). Nevertheless, diffusion-weighted MR imaging remains sensitive for identification of pus and is better than conventional sequences for evaluation of abscess therapy because restricted diffusion has been shown to correlate with residual or recurrent pus (29).

The differential diagnosis of a ring-enhancing lesion at postcontrast MR imaging (Fig 3d, 3e) is broad. Although a continuous smooth thin (2–7-mm) ring is highly characteristic of a pyogenic abscess, it is not a specific finding (30). Sometimes, neoplasms, demyelinating disease, and vascular injury have a similar appearance. Neoplasms usually have a more nodular and irregular appearance, and demyelinating disease may have a more classic asymmetric comma-shaped peripheral-enhancement pattern.

MR spectroscopy may be useful for the evaluation of necrotic masses. The central necrosis cavity shows absence of normal brain metabolites (choline, creatine, and N-acetyl aspartate). In a series of 194 pyogenic brain abscesses, MR spectroscopy revealed an elevated amino acid level (0.9 ppm) as a marker of proteolytic enzymes from neutrophils in 80% of cases, with a sensitivity of 0.72 and specificity of 0.30 (31).

In addition to the subarachnoid space and brain parenchyma, pyogenic bacteria can infect the ventricles (ventriculitis or pyocephalus) and extra-axial potential spaces (epidural or subdural empyema). Similar to parenchymal abscess, pus in the ventricles (occipital horns) or epidural or subdural space shows restricted diffusion, a finding that is useful for distinguishing simple effusion from empyema in the context of acute bacterial meningitis (Fig 4c, 4d). Intraventricular, epidural, or subdural blood may also show restricted diffusion, although correlation with the clinical history and head CT findings can usually help differentiate hemorrhage from infection. Pyogenic ventriculitis is a frequent complication of meningitis in infants but is relatively
Figure 3. Abscess. (a) Axial T2-weighted MR image shows two focal masses (arrows) in the posterior left cerebral hemisphere with peripheral well-defined hypointense margins (correlating with capsule formation) and surrounding hyperintensity consistent with vasogenic edema. (b) Axial diffusion-weighted MR image reveals hyperintensity of both masses. (c) Axial apparent diffusion coefficient MR image shows corresponding hypointensity indicative of restricted diffusion. (d) Axial T1-weighted MR image shows central hypointensity of both masses and a thin perimeter of slight hyperintensity (arrowheads). (e) Axial contrast-enhanced T1-weighted MR image reveals corresponding enhancement of the margins of both masses.
uncommon in adults; risk factors such as craniotomy or diabetes predispose to *Staphylococcus* and *Enterobacter* infections. Typical CT and MR imaging findings include intraventricular debris, ventricular dilatation, and periventricular edema; the presence of intraventricular restricted diffusion or periventricular enhancement is dependent on whether the patient can mount an inflammatory response (32). Both epidural and subdural empyemas are rim-enhancing purulent collections (Fig 4a and 4b) that arise from nearby infection, but the latter is more likely to cause complications, such as thrombophlebitis or cerebritis, and therefore requires urgent neurosurgical intervention (33–36). Subdural empyemas have been reported to show restricted diffusion more often than do epidural empyemas, although exceptions to the rule certainly exist (37).

**Atypical Bacterial Infections**

**Tuberculosis**

In contrast to the aforementioned more typical bacterial pathogens, in which the intense cellular debris created by polymorphonuclear phagocytes is seen, atypical pathogens survive and evade the acute inflammatory response, in many cases, by hiding intracellularly. Consequently, these diseases usually lack suppuration and instead recruit mononuclear phagocytes (monocytes), which mature into organized collections of macrophages (granulomas) in a more
chronic disease process. Granulomatous inflammation is a method to block and destroy the foreign invaders, while sensitizing the adaptive immune system through antigen presentation by lymphocytes. Granulomas with caseating necrosis are typical of tuberculosis, which is arguably the prototypical atypical bacterial infection. The high mycolic acid content of the mycobacterial cell wall is responsible for many of the following unique features of these organisms: they hide and grow in macrophages as immune evasion, are acid fast at histologic staining, correlate with elevated lipid levels at MR spectroscopy, and play a key role in subsequent induction of granulomatous inflammation (38).

*Mycobacterium tuberculosis* was isolated by Robert Koch in 1882, and he received a Nobel Prize in 1905 for this discovery. This slowly dividing facultative intracellular pathogen has plagued mankind for thousands of years and continues to be the cause of approximately 1.7 million deaths per year. An estimated 2 billion persons worldwide have latent infection, in which the immune system is able to contain mycobacterial replication but with approximately 10% lifetime risk for development of active symptomatic tuberculosis. *M tuberculosis* can hide and divide in macrophages at a very slow rate (doubling every 15–20 hours); therefore, performance of diagnostic cultures and administration of therapeutic regimens are difficult and time consuming and have been recently complicated by the emergence of drug-resistant infection, HIV infection, and AIDS (39). Transmission occurs through respiratory droplets; thus, active infection usually begins in the lung as a Ghon focus, the primary parenchymal lesion in primary pulmonary tuberculosis. Constitutional symptoms, including night sweats and weight loss (consumption), accompany pulmonary symptoms. Hematogenous dissemination may cause extrapulmonary manifestations, including cortical granulomas (Rich focus) in the brain; these granulomas are more common in young children or immunocompromised individuals and may rupture in the subarachnoid space and cause tuberculous meningitis. Miliary tuberculosis is more common in children and, although still controversial, is believed to be directly involved in the pathogenesis of tuberculous meningitis (40).

Prevention through vaccination began with the bacille Calmette-Guérin vaccine in 1921; this vaccine includes an attenuated strain of *Mycobacterium bovis* and was developed by Albert Calmette and Camille Guérin. Despite being the most widely used vaccine in the world (four billion doses total by 2011), the tuberculosis pandemic has not been contained because of the vaccine’s variable efficacy; it is less effective against adulthood pulmonary tuberculosis but more effective against childhood tuberculous meningitis (39). Treatment options were limited until the discovery of streptomycin in 1946 by Selman Waksman, for which he received a Nobel Prize in 1952 (41). Modern treatment regimens include isoniazid and rifampicin (39).

Neuroimaging manifestations of tuberculous meningitis include characteristic thick or nodular enhancement in the basal cisterns (Fig 5), although this finding may also be noted in meningitis due to other granulomatous (fungus...
or sarcoïd) and neoplastic (carcinoma or lymphoma) diseases. Common sites of this enhancement include the cistern of the lateral cerebral fossa (where the M1 segment of the middle cerebral artery is located) and the sylvian fissure. Associated inflammation or vasospasm in the penetrating vessels through the involved region may result in basal ganglia infarction (42). Other possible sequelae of tuberculous meningitis include hydrocephalus, which is common and usually communicating, and cranial neuropathy due to extension of cisternal inflammation along the traversing cranial nerves (43). On rare occasions, tuberculosis can seed the bone or dura and thus produce pachymeningitis (44).

A tuberculoma is the most common parenchymal form of tuberculosis and typically manifests as a lesion with well-defined hypointensity and solid or ringlike enhancement at T2-weighted imaging. These lesions may be single or multiple. Central nonenhancing high signal intensity at T2-weighted imaging depends on the extent of liquefaction or caseation (44). Some cases may show the “target sign,” with a small focal area of calcification or enhancement in the center of a ring-enhancing mass; this finding was once believed to be pathognomonic for a tuberculoma granuloma but has since been proven to be nonspecific (45). Magnetization transfer imaging improves detection of meningeal or parenchymal disease at pre–gadolinium-enhanced imaging. Magnetization transfer ratios in tuberculosis are lower than those in pyogenic infections and higher than those in viral infections, with the difference related to variations in protein content (46). Tuberculomas are reported to demonstrate lipid level peaks at 0.9 ppm, 1.3 ppm, 2.0 ppm, and 2.8 ppm at MR spectroscopy; these peaks are believed to correlate with the presence of the high lipid content of the mycolic acid in the mycobacterial cell wall, as described earlier. Although noted in pyogenic abscesses, amino acid resonances at 0.9 ppm are not seen in tuberculous abscesses, presumably because of absence of neutrophil proteolysis (47).

In general, a tuberculoma granuloma has less surrounding vasogenic edema than does a tuberculous abscess, which is also usually larger (44). Early rapid clinical deterioration, particularly in an immunocompromised patient, favors the presence of an abscess on a clinical basis. Distinguishing a caseating tuberculoma from the much less common tuberculous abscess at imaging may be difficult (compare Figs 6 and 7); however, presence of numerous tubercle bacilli and absence of tubercular granulomatous formation in the abscess at histopathologic examination are more definitive findings.

**Spirochetal Diseases**

A second category of atypical bacteria comprises the pathogenic spirochetes, which are long, thin, spiral-shaped extracellular microorganisms in which internal flagella result in twisting locomotion. They evade the immune system through antigenic variation and other strategies; local mucocutaneous infection gradually progresses to chronic systemic disease, which has been called “The Great Imitator” of other neoplastic or autoimmune conditions. Although syphilis (caused by *Treponema pallidum*) may be linked to Christopher
Columbus’ return voyage to Europe in 1493, at present the more recently discovered systemic borreliosis has attracted more interest in neuroimaging, particularly in the United States (48).

In 1975, a cluster of juvenile rheumatoid arthritis–like cases centered around the small towns of Lyme and Old Lyme, Connecticut, and was connected to prior tick bites and rash (erythema migrans) (49). In subsequent investigations, Willy Burgdorfer, a Swiss-born and -educated bacteriologist working in the United States, isolated a unique Borrelia species, now known as Borrelia burgdorferi, as the causative agent (49). Today, Lyme disease is recognized as a heterogeneous zoonosis, with geographical variation in the animal reservoir, the tick species, and the spirochete sub-species. In the United States, Borrelia burgdorferi sensu stricto has a predisposition for hematogenous dissemination and may cause lymphocytic arthritis and meningitis. In Europe, borreliosis due to Borrelia garinii spreads along peripheral nerves and thus may cause painful meningo-radiculitis (Bannwarth syndrome) (50). Many cases of Lyme disease have no neuroimaging manifestations.

Smooth abnormal leptomeningeal enhancement with cranial or spinal nerve involvement may be seen but may not correlate with clinical neurologic deficits. Perivascular extension of the lymphocytic inflammation may lead to enhancing periventricular, callosal, and infratentorial white matter lesions that are reminiscent of multiple sclerosis, except for the leptomeningeal enhancement (51).

Figure 7. Tuberculoma. The constellation of findings often overlaps with those of tuberculous abscess. (a) Axial T2-weighted MR image shows a nodular mass (arrow) in the right midbrain with peripheral hypointensity and surrounding hyperintensity consistent with vasogenic edema. (b) Axial contrast-enhanced T1-weighted MR image reveals associated peripheral enhancement (arrow). (c) Axial T2-weighted MR image shows a larger and more heterogeneous mass of the paramedian left frontoparietal region with characteristic central hypointensity (arrowheads) and generous surrounding hyperintensity consistent with vasogenic edema. (d) Axial contrast-enhanced T1-weighted MR image shows intense but irregular enhancement.
The term syphilis (from the Greek syphlos, meaning crippled) is derived from a poem by Girolamo Fracastoro in 1530 that is entitled “Syphilis or the French Disease”; it describes a shepherd who complained about the sun god and was punished with a hideous disease. T pallidum may be transmitted sexually or placently; a painless cutaneous ulcer (chancre) is the hallmark of primary syphilis. Similar to neuroborreliosis, neurosyphilis is a consequence of hematogenous dissemination; the risk of progression has decreased from 30% to 3% because of the current availability of penicillin. Symptomatic types of neurosyphilis include meningeal (latent period <2 years), vascular (5–7 years), general paresis (10–20 years), and tabes dorsalis (15–20 years). Progression may be accelerated in patients with cell-mediated immunodeficiency, such as those with HIV infection or AIDS (52). Syphilitic meningitis may be thick and nodular with gummas, similar to other granulomatous diseases (such as tuberculosis or sarcoidosis). Vascular neurosyphilis is characterized by an arteritis affecting large vessels more than small vessels, with alternating stenoses and dilatations at angiography and large- or small-vessel infarctions at neuroimaging. Parenchymal edema may also result from perivascular extension of subarachnoid infection or from rare deposition of cerebral gummas (53).

Early borreliosis and syphilis are easily treated with a few weeks of antibiotics; unfortunately, early diagnosis is difficult without a history of tick bite, erythema migrans, sexual exposure, or chancre. Both spirochetes are fastidious or difficult to determine at culture, and detection relies on serologic test results (antibody titers). Even after successful diagnosis of B burgdorferi infection, 10%–20% of patients experience posttreatment Lyme disease syndrome due to autoimmune effects of molecular mimicry and antigen cross-reactivity (54).

Rickettsial Disease
A third category of atypical bacteria that is also responsible for vector-borne disease is Rickettsia, which is a genus of obligate intracellular pathogens that behave similarly to viruses and is the closest living relative of mitochondria. The organism is named for Howard Taylor Ricketts, who studied Rocky Mountain spotted fever and then died of another rickettsial disease (typhus) while investigating a disease outbreak in Mexico City in 1910. In Rocky Mountain spotted fever, caused by Rickettsia rickettsia, endothermal tropism leads to both the classic petechial rash (observed in approximately half of patients) and destructive systemic thrombovasculitis (55). Similar to the tick-borne Lyme disease, Rocky Mountain spotted fever has a geographic and seasonal distribution, with most cases occurring from April through September and not limited to the Rocky Mountain region, despite the name (in 2010, 60% of cases occurred in five southern states) (56). Transmission of the organism from tick to host requires at least 24 hours of attachment, and initial flu-like symptoms can progress to meningoencephalitis. Rocky Mountain spotted fever is the most common and lethal rickettsial infection. With the availability of tetracycline and chloramphenicol therapy, mortality has decreased from 28% in 1944 to less than 1% beginning in 2001 (56). Neuroimaging findings in affected patients are usually normal. However, abnormal leptomeningeal enhancement, signal abnormality in the perivascular spaces, and cerebral edema or infarcts related to small-vessel disease are possible and represent relatively unfavorable prognostic indicators (57).

Fungal Infections
In contrast to pyogenic and atypical bacteria, fungi (from the Latin fungus, meaning mushroom) are eukaryotic saprotrophic organisms with membrane-bound nuclei that derive nutrition from decomposition of organic matter. Fungal diseases of the CNS are usually opportunistic infections resulting from hematogenous dissemination in susceptible hosts, such as patients at extremes of age or with immunodeficiency. There are behavioral similarities to mycobacteria (from the Greek mykes, meaning mushroom), which also produce granulomatous inflammation and originally infect the respiratory tract. However, unlike tuberculosis, pulmonary fungus is not transmitted from person to person by respiratory droplets but is acquired through inhalation of fungal spores from environmental soil.

Yeasts
Fungal pathogens can be divided into three basic morphologic categories or growth patterns—yeast, mold, and dimorphic fungus—that influence pathophysiology and neuroimaging patterns (58). Approximately 1% of fungal species are yeasts, which are unicellular eukaryotic microorganisms that reproduce by asymmetric fission (i.e., budding). Because of their large cell size and fermentation, yeasts played a central role in the early development of microbiology and biochemistry; “yeast” often refers to Saccharomyces cerevisiae, which remains important to modern cell biology research and to the brewing of ale or baking of bread (59). Yeast pathogens, especially Cryptococcus neoformans and Candida albicans, commonly cause opportunistic infections in immunocompromised patients. However, on rare occasions, less common pathogenic
species, such as *Cryptococcus gattii*, may cause disseminated infections in immunocompetent hosts (60).

*C neoformans* is a ubiquitous organism found in bird feces (pigeon droppings), and cryptococcosis begins with inhalation of its reproductive spores. *C neoformans* has a unique protective polysaccharide capsule that produces a characteristic halo with India ink stain. *C albicans* is a normal constituent of the gut flora; candidiasis (candidosis) may manifest as superficial overgrowth (thrush) or invasive systemic disease.

Unicellular yeasts, such as *Cryptococcus*, are small enough to enter the meningeal microcirculation through hematogenous dissemination. Cryptococcal meningitis is the most common fungal disease of the CNS, and its frequency is believed to be related to the presence of essential nutrients and the absence of serum inhibitor in the CSF (61). Similar to other hematogenous granulomatous infections, possible neuroimaging patterns include abnormal leptomeningeal enhancement, which may have a nodular appearance, and parenchymal cryptococcomas (Fig 8), which may be miliary (<3 mm) or larger. In cryptococcal infection, budding yeast and mucoid material expand the perivascular spaces, producing gelatinous pseudocysts that are typically seen in the basal ganglia (Fig 9) (62). Edema and enhancement
may be attenuated in the context of immunodeficiency or corticosteroid therapy (63).

*C. albicans* infection is the most common nosocomial fungal infection; it is particularly common in patients receiving immunosuppressive therapy or with indwelling catheters. *Candida* has the ability to transform from yeast to a pseudohyphal form that can cause more invasive parenchymal disease. Accordingly, disseminated disease may result in scattered cerebral microabscesses (<3 mm) or angioinvasion with thrombosis and hemorrhage, but macroabscesses and meningitis are uncommon (64). The differential diagnosis for candidal microabscesses includes *Staphylococcus aureus* infection, *M. tuberculosis* infection, metastatic disease, and multiple sclerosis (65).

**Molds**

Unlike yeasts, molds grow as multicellular filaments (hyphae), which can form into macroscopic networks (mycelia). A continuous growth of mycelium (*Armillaria ostoyae*) in eastern Oregon has been called the largest organism in the world, spreading underground and spanning 2200 acres (“Humongous Fungus”). In 1928, a rare mold (*Penicillium notatum*) drifted into Alexander Fleming’s messy laboratory while he was on vacation, settling at the edge of a petri dish and killing nearby staphylococcal colonies. After noticing this when he returned to the laboratory, he spent the next decade studying “mould juice,” which he named penicillin. The problem of concentrating and purifying this substance for mass production was eventually solved by Howard Florey and Ernst Chain. For their collective efforts, these three scientists shared a Nobel Prize in 1945 (66).

Not all molds are comical or beneficial. Pathogenic molds include *Aspergillus* and *Mucorales* species. Similar to *Cryptococcus* species, these filamentous fungi are ubiquitous in the soil and can infect the respiratory tract after spore inhalation. Unlike yeast, the multicellular hyphae are too large for the meningeal microcirculation and instead are more likely to cause invasive parenchymal disease in immunocompromised patients.

Cerebral aspergillosis and mucormycosis may originate from hematogenous dissemination from a distant pulmonary infection, angiotropic or perineural spread from a paranasal sinus or orbital infection (rhinocerebral disease), or direct traumatic implantation (67). Aspergillosis is more likely to manifest with ring-enhancing cerebral abscesses from hematogenous dissemination (68). The presence of intracavitary projections that are hypointense on T2-weighted MR images and apparent diffusion coefficient MR images without associated enhancement is characteristic of fungal abscesses (correlating with proliferating hyphae) and may allow distinction from pyogenic or tubercular abscesses (69). Mucormycosis is more likely to manifest as rhinocerebral disease in immunocompromised or diabetic patients because of a locally aggressive sino-orbital infection (69). Both aspergillosis and mucormycosis have a propensity for vascular invasion by fungal hyphae (facilitated by production of elastase); this may result in cerebral infarction, hemorrhage, or mycotic aneurysm (Fig 10) (70,71). Both are life-threatening conditions, and survival depends on early diagnosis, surgical débridement, and administration of intravenous antifungal therapy.

**Dimorphic Fungi**

The third category of fungal organisms is dimorphic fungus, which grows as mold at room temperature and as yeast at body temperature. Conversion between the two phases at 25–30°C and 35–37°C is a traditional method for identifying these organisms at fungal culture (72). Because *Blastomyces dermatitidis*, *Coccidioides immitis*, and *Histoplasma capsulatum* are unicellular eukaryotes at body temperature, they were initially misidentified as protozoa. Outside the body, they are multicellular mycelia (molds) that reside in the soil in regions where they are endemic and release conidia (spores) into the air. Spore inhalation may lead to acute respiratory illness, chronic nodular or fibrocavitary pulmonary disease, or disseminated disease. Chronic pulmonary or disseminated disease requires antifungal therapy, such as long-term oral fluconazole or intravenous or intrathecal amphotericin (73).

Coccidioidomycosis is endemic in the southwestern United States and arid regions in Latin America. Much of what is known about the disease is derived from the work of Charles Smith, who studied cases in San Joaquin Valley in central California during the Great Depression (in migrant farmers from the “Dust Bowl” of the Midwest) and World War II (primarily in military recruits, Japanese-Americans at internment camps, and Axis-powers combatants at prisoner-of-war camps) (74). He found a higher incidence when a wet season (allowing for robust growth of the mold) was followed by a dry season (allowing for spore dispersal in the dust). Exposure led to primary pulmonary disease (valley fever) in 40% of patients, chronic pulmonary disease in 5%–10%, and disseminated disease affecting the skin, bones, and meninges in 1%. Smith noticed that individuals of African or Filipino descent were less likely to develop valley fever but more likely to develop disseminated
Figure 10. Mucormycosis with bilateral necrotic masses involving deep gray matter structures. (a) Initial axial CT image shows focal hypoattenuation (arrows) in the left caudate head and lentiform nucleus. (b) Initial axial T1-weighted MR image reveals a hypointense mass in the left caudate head and lentiform nucleus. (c) Initial axial T2-weighted MR image shows corresponding but heterogeneous hyperintensity and some regions of hypointensity. (d) Initial axial contrast-enhanced T1-weighted MR image slightly more superior to b depicts minimal enhancement along the margins of the mass. (e) Follow-up axial T1-weighted MR image (obtained 4 days later) shows new bilateral involvement. (f) Follow-up axial T2-weighted FLAIR MR image reveals more conspicuous hypointense regions correlating with heavier concentrations of fungal elements and/or hemorrhage. (Fig 10 continues.)

During an infection, *Coccidioides immitis* and its close relative *Coccidioides posadasii* transition into spherules (not yeast) and then reproduce by rupturing and releasing endospores (instead of budding). Similar to yeasts and in contrast to hyphal fungi, these tiny endospores are more likely to result in meningitis than in parenchymal granulomas or abscesses. Fungal meningitis occurs in half of disseminated coccidioidomycosis cases and is even less common in histoplasmosis and blastomycosis. The neuroimaging pattern of coccidioidomycosis is similar to that of tubercular meningitis, with thick exudate and abnormal enhancement in the basal cisterns and subarachnoid space that may be complicated by hydrocephalus or vasculitis. Vasculitis is observed in up to 40% of cases, most commonly involving small perforators and resulting in deep brain infarcts (75). Subarachnoid hemorrhage resulting from granulomatous inflammation of large vessels has been reported (76). In addition to meningitis and vasculitis, cerebritis may develop (especially in immunocompromised patients) as a result of fungal extension along vessel walls or in perivascular spaces (77).
Parasitic Infections

Species interactions can be mutualistic, commensalistic, or parasitic, depending on whether the relationship benefit both entities, one entity alone, or one entity at the expense of the other. Although all infectious pathogens can be considered to be parasites of the human body, this section will focus on parasites derived from mobile eukaryotic heterotrophs, which may be unicellular protozoa (from Greek protos zoion, meaning first animal) or multicellular helminths (from Greek helmins, meaning worm). The most common of these parasitic infections in the United States are cysticercosis, echinococcosis, and toxoplasmosis. Amebiasis, malaria, and schistosomiasis may also occur but are less common.

Neurocysticercosis

Neurocysticercosis is caused by infection due to the pork tapeworm Taenia solium after fecal-oral contamination from a tapeworm carrier of infective embryos that cross the intestinal mucosa, move into the capillary system, and become mature larval cysts (scolices) in the brain, muscles, and other sites, usually in less than 3 months. The disease is distinct from taeniasis, which is caused by ingestion of raw or undercooked pork and is confined to the intestinal tract (78). In the United States, the disease was originally limited to the southwestern region but has become more widely distributed over the past 30–40 years (78).

Although patients with neurocysticercosis are frequently asymptomatic during the early stages of the disease, they commonly develop seizures (50%–70%), headaches (43%), and findings related to hydrocephalus (30%) when the scolices begin to die or from cysts in the ventricular system (79–81). Most symptomatic patients are 15–40 years of age, and there is no sex or race predilection (82). Clinical findings related to diffuse encephalitis are more common in young females, children, and patients receiving antihelminthic therapy (usually albendazole and praziquantel) (78). Arachnoiditis, meningitis, cranial nerve palsies, and cerebrovascular complications (usually as lacunar infarctions) may also be affiliated with the disease. Less commonly, more geographic-specific effects of the disease are seen, such as an intraventricular cyst (Fig 11a, 11b) obstructing
Figure 11. Neurocysticercosis imaging findings in four different patients. (a) Axial contrast-enhanced T1-weighted MR image in patient 1 shows a well-circumscribed cyst-like mass in the left lateral ventricle near the foramen of Monro with associated ventricular dilatation and periventricular hypointensity (arrows), findings compatible with reversal of transependymal CSF flow due to acutely increased intraventricular pressure. (b) Gross specimen from patient 1 shows a multilobulated cyst with internal soft tissue representing the scolex. (c) Axial contrast-enhanced T1-weighted MR image in patient 2 shows numerous nonenhancing cyst-like masses in the basal cisterns that were pathologically proven to be racemose cysts. (d) Axial T1-weighted MR image in patient 3 reveals corresponding hypointensity, with some lesions showing internal soft-tissue signal intensity (arrowheads) indicative of scolices. (e) Axial T2-weighted MR image in patient 3 shows highly characteristic multifocal nodular masses (one of which is shown by the arrow) throughout the cerebral hemispheres with hyperintensity and some with surrounding vasogenic edema. (f) Axial contrast-enhanced T1-weighted MR image in patient 3 shows ringlike enhancement of numerous lesions. The combination of findings in this patient is indicative of the colloidal vesicular stage. (g) Axial CT image in patient 4 depicts numerous calcified lesions, reflective of the calcified nodular stage of the disease.
ventricular flow and causing headache, papilledema, and loss of consciousness (Bruns syndrome) or from multiple areas of ischemic injury involving the midbrain and thalamus from occlusion of vessels traversing the cisterns (progressive midbrain syndrome) (80,81). Cysticercus-specific immunoglobulin G antibody testing or enzyme-specific immunoabsorbent assay of serum or CSF samples may provide additional support for the diagnosis (83).

The stages of parenchymal neurocysticercosis are well documented (84). In the vesicular stage, the parasite resides quiescently in the brain parenchyma as a small nonenhancing cyst protected by a cyst wall rich in glycoproteins that provides an effective barrier from the surrounding tissue, without surrounding edema. CT and MR imaging findings of cysts in this stage are consistent with fluid. The presence of the scolex in such a cyst may create a “target” or “dot in a hole” appearance because the slight soft-tissue attenuation and signal intensity in the larva help distinguish it from surrounding fluid (Fig 11d). The vesicular colloidal (sometimes also referred to as the colloidal vesicular or colloidal) stage is characterized by the death of the scolex from natural processes or from effects of therapy with associated disruption of the cyst wall (84). As a consequence, an intense inflammatory reaction to the then unprotected and decaying parasite results in altered signal intensity, compared with CSF. At T2-weighted FLAIR MR imaging, this reaction is particularly conspicuous related to the developing proteinaceous and gelatinous debris and typically substantial surrounding edema (Fig 11e). A ringlike pattern of enhancement is often evident at postcontrast T1-weighted imaging (Fig 11f). In this stage, the severity of the inflammatory process may result in diffuse encephalitis and the presence of extensive disease may dictate therapeutic management (78). The granular nodular stage begins with cyst retraction and formation of a granulomatous nodule with surrounding gliosis (84). Calcification of this nodule demarcates the calcified nodular stage as the last (and nonactive) stage of neurocysticercosis (Fig 11g) (79). Any remaining edema or enhancement at neuroimaging resolves during this stage. Multiple lesions corresponding to varying stages of the disease are typical.

Occasionally, a grape-like cluster of cysts (racemose form) (Fig 11c) without scolices may arise in the cisterns and sylvian fissure and does not show associated enhancement or progression through the stages described above (81). Arachnoiditis and vasculitis have also been documented with corresponding neuroimaging features (78).

Toxoplasmosis
Toxoplasmosis, which is caused by Toxoplasma gondii, an obligate intracellular protozoan parasite, is the most common opportunistic infection affecting the CNS in patients with AIDS (85). During its life cycle, T gondii manifests in three forms: the cyst (bradyzoite), trophozoite, and oocyst, which is uniquely found in the intestinal mucosa of cats. Once outside the feline host, the oocyst can survive for at least a year in warm moist soil (85). Birds, mammals, and reptiles may also serve as hosts. Cockroaches and fleas are other potential reservoirs (85). Human exposure shows a geographic variation, with the highest rates in France (75%–90%) and Central America, and rates of 17%–35% have been reported in cities in the United States (85,86).

Fecal-oral transmission via fruits, vegetables, or poorly cooked meat is the usual route of disease spread to humans, although hematogenous transmission through blood transfusion is also possible (85). It is estimated that approximately 500 million persons are infected with T gondii worldwide. Children are particularly susceptible to infection after encounters with a house cat or litter box. After the organism is ingested, Toxoplasma cysts may occur in any tissue but are most common in the brain, retina, skeletal muscle, and cardiac muscle. Although fever, rash, lymphadenopathy, and eye disturbances are typical in early stages, the disease is often self-limited. However, the disease may be transmitted transplacentally and have devastating effects on the fetal brain because maternal antibodies passed to the child will be limited by the blood-brain barrier. Seizures, microcephaly, and chorioretinitis are noted in most cases (85).

After the human host is infected, the disease remains dormant for as long as normal host immunity is maintained. However, immunocompromised patients are susceptible to active proliferation of the parasite, with local necrosis and dissemination. When lesions are in the CNS, fever, headaches, confusion, and seizures are common, and 20% of HIV-infected patients with toxoplasmosis develop encephalitis (85).

Neuroimaging studies in patients with toxoplasmosis commonly show multifocal abscesses with a predilection for the basal ganglia. However, solitary lesions have been noted in about one-third of patients (Fig 12). Most lesions show enhancement, often in a ringlike pattern. Although it occurs in less than 30% of cases, the eccentric target sign, which is related to a small enhancing nodule along the lesion margin (Fig 12d), has been reported to be highly suggestive of a diagnosis of toxoplasmosis (85). In distinction to the well-defined enhancing wall seen
in bacterial abscess formation, toxoplasmosis abscesses may have poorly defined peripheral enhancement in immunocompromised patients; this finding is believed to reflect a poor host response to the infection. Diffuse cerebral volume loss is seen in approximately 30% of cases and likely reflects changes related to superimposed HIV infection (85).

The imaging appearance of toxoplasmosis may overlap that of CNS lymphoma and other neoplasms. Subcortical location, eccentric target sign, absence of corpus callosal or leptomeningeal involvement, and marked edema are imaging findings that favor toxoplasmosis, whereas hyperattenuation, hypointensity on T2-weighted images, restricted diffusion, and periventricular location favor CNS lymphoma (85,87).

If toxoplasmosis is suspected on the basis of clinical and neuroimaging findings, an empirical trial of antitoxoplasma therapy for 2–3 weeks may prove to be definitive. An interval decrease in size of the lesion by the end of the trial is considered to be sufficiently confirmatory to continue therapy and neuroimaging surveillance until the lesion completely resolves. Stable or increasing size of the lesion may be indicative of an alternate diagnosis, especially CNS lymphoma, and performance of a tissue biopsy for a definitive diagnosis may be necessary. Metabolic imaging may permit a more timely distinction between toxoplasmosis and CNS lymphoma because of the latter’s greater propensity for hypermetabolic activity compared with toxoplasmosis, which more commonly involves hypo- or isometabolic activity (85,87).

Figure 12. Toxoplasmosis. (a) Axial T1-weighted MR image shows a broad mass effect related to a hypointense mass (arrows) in the right occipital lobe. (b) Axial T2-weighted FLAIR MR image reveals generous hyperintensity surrounding the mass (arrows) that is consistent with vasogenic edema. (c) Axial contrast-enhanced T1-weighted MR image shows intense ringlike enhancement (arrows). (d) Coronal contrast-enhanced T1-weighted MR image better depicts characteristic eccentric nodular enhancement (arrowheads) along the superior margin.
Echinococcosis

Echinococcosis, caused by *Echinococcus* infestation, is a zoonotic parasitic disease believed to infect more than 1 million persons worldwide, with 1–3 million DALYs annually due to cystic echinococcosis and 650,000 DALYs annually due to alveolar echinococcosis (88). There are two forms of the disease that are most relevant to human hosts. Cystic echinococcosis, also known as hydatid disease, is caused by *Echinococcus granulosus,* a tapeworm found in dogs (the definitive host) and sheep, goats, and swine (intermediate hosts) (89). Through fecal-oral contamination, embryonated eggs hatch in the intestines and release oncospheres that penetrate the intestinal wall, enter the circulatory system, and eventually produce maturing cysts in target end organs, most prominently the lungs and liver but also the heart, spleen, bones, and CNS (89). Although many affected humans are asymptomatic, hepatic cyst enlargement eventually causes pain, nausea, and vomiting; chronic cough, chest pain, and shortness of breath are affiliated with lung cysts (88,89).

Rupture of the cysts may occur after trauma and may cause mild to severe anaphylactic reactions, with death possible in rare cases (89). Chemotherapy, cyst puncture, and PAIR (puncture, aspiration, injection of ethanol, and reaspiration) have replaced surgery in many cases, although surgical resection provides the greatest chance for complete cure (89). Cerebral lesions occur in 1%–4% of individuals with cystic echinococcosis, with nonspecific clinical findings related to increased intracranial pressure and seizure activity (90). Cystic echinococcosis has been reported on all continents except Antarctica and is endemic in many sheep- and cattle-raising countries (88,90).

Alveolar echinococcosis is a more serious and dangerous form of echinococcosis that is caused by *Echinococcus multilocularis.* Foxes are the definitive hosts, and small rodents are the intermediate hosts. This tapeworm primarily affects the liver, with secondary involvement of the lungs and brain (reported in 1% of cases) (89,91). Persistence of the larval forms (without cyst maturation) leads to vesicles and destruction of surrounding tissues (89). The mortality rate associated with alveolar echinococcosis varies from 50% to 75%, with higher rates related to older age and poor local health care for affected individuals (89). Therapy is more difficult for this form of the disease and includes radical surgery and/or long-term albendazole therapy (89). Alveolar echinococcosis is reported to be limited to the Northern Hemisphere, with a predominance of cases in western China (89).

Neuroimaging manifestations of cystic echinococcosis include a well-defined oval or round mass or masses in the brain parenchyma, frequently in the parietal lobe, with attenuation and signal intensity similar to those of CSF and a characteristic but occasional hypointense rim at T2-weighted imaging, without associated enhancement (Fig 13) (90,92). The presence of multiple cysts suggests the rupture of a preexisting single cyst (90). A faint surrounding halo of hyperintensity at T2-weighted imaging is occasionally noted and is believed to reflect the pericyst, the outermost layer of the cyst, composed of inflammatory cells and fibrous tissue (92). Less commonly, surrounding edema may also be present (92). Rumboldt and colleagues (92) reported a heterogeneous predominantly cystic mass with a fluid-debris level correlating with pathologically proven hydatid sand, a whitish sediment created by rupture of the scolices that line the true cyst wall (Fig 13b). Rupture or infection of the cyst may alter the imaging appearance, with slightly decreased signal intensity at T2-weighted imaging and increased signal intensity at T1-weighted imaging (92). A single case report of a hydatid cyst in a human host showed elevated succinate, lactate, alanine, acetate, and pyruvate levels at MR spectroscopy (93). Rarely, the lesion may involve the dura, subarachnoid space, ventricular system, brainstem, and spinal canal (92,94–96).

Neuroimaging manifestations of alveolar echinococcosis lesions frequently include heterogeneous solid, partially solid, or cystic masses with calcification at CT and corresponding hypointensity at T1- and T2-weighted MR imaging (91). Prominent surrounding edema is common, and heterogeneous ringlike, nodular, and cauliflower-like enhancement is typical (91). Perfusion MR imaging has shown decreased relative cerebral blood volume in the central portion of the lesion and higher relative cerebral blood volume in the periphery, a finding likely reflecting inflammation (91). MR spectroscopy of alveolar echinococcosis in an animal model has shown an elevated succinate level in addition to elevated acetate, alanine, creatine, glycine, and lactate levels (97). Other investigators (91) have demonstrated normal N-acetylaspartate-to-creatine and choline-to-creatine ratios in a pathologically proven alveolar echinococcosis lesion; this finding may help differentiate similar lesions from neoplasms. Disseminated lesions in the terminal phase of the disease may occur (91). Although the imaging appearance of alveolar echinococcosis often mimics that of a cerebral neoplasm, the presence of multicystic liver disease should at least raise the possibility of the diagnosis (91).
Amebic Infections
Amebas are free-living protozoa that are widespread in water, soil, and air worldwide (98). Although many of these organisms are nonpathogenic, some species are known to cause severe and frequently devastating infections in both animals and humans, particularly in the CNS (99). For reasons that are not entirely clear, the prevalence of infection due to these organisms has increased substantially since the late 1980s (98,99). Although amebic infections are uncommon, compared with bacterial and fungal infections, they are noteworthy for their extreme virulence and very high mortality rates.

Granulomatous Amebic Encephalitis
Acanthamoeba and Balamuthia species cause granulomatous amebic encephalitis usually in immunocompromised patients, including those receiving monoclonal antibody therapy, but may rarely occur in immunocompetent hosts (99–102). Disseminated granulomatous amebic disease and amebic keratitis are other forms of the disease (100).

Acanthamoeba species are believed to affect the CNS through hematogenous spread from the skin or lower respiratory tract, with the blood-brain barrier as the likely site of infection (103). The prevalence of the disease is probably underestimated because of the difficulty in establishing the diagnosis before death and the erroneous ascribing of the patient’s condition to “pyogenic meningoencephalitis” without consideration of an amebic infection (99,104).

Balamuthia mandrillaris is another free-living ameba. It was initially reported in a pregnant
mandrill baboon that died at the San Diego Wild Animal Park in 1989, and the first known human host was described in 1990 (105). The ameba is found in the soil and is transmitted through inhalation of airborne cysts, direct contamination of a skin lesion, or organ transplantation (106–108). Exposure to soil, either from occupational (eg, agriculture or construction) or recreational (eg, dirt biking or gardening) contact, is common (106). Stagnant water is another possible source (106). Hispanic individuals account for a disproportionate percentage of cases (nearly 50%) in the United States, data possibly reflecting environmental, genetic, or socioeconomic factors (106). A predilection for southern California and other states with a warm climate (especially Texas, Georgia, and Florida) has been noted (106). Similar to Acanthamoeba infections, early reported cases occurred in immunocompromised hosts, although cases in immunocompetent patients have more recently been reported. At least 150 cases have been reported worldwide (109). The age range of infected patients is wide (2–84 years of age in the California Encephalitis Project cohort) (106).

The clinical manifestation of Acanthamoeba infection is typically subacute to chronic encephalitis, commonly with headache, altered mental status, and focal neurologic deficits (100). Diagnosis of Acanthamoeba infection can be established through a variety of tests, including identification of trophozoites with “spikey” pseudopodia on wet mount and Giemsa stains of CSF samples and positive polymerase chain reaction test results (100). An overwhelming majority of affected patients die of the disease, with only a few survivors reported in the literature (100,110–112). No definitive therapy has been reported in the literature, although combination antibiotic, antifungal, and antihelminthic treatment (typically rifampicin, fluconazole, and trimethoprim-sulfamethoxazole) is commonly given (100). Despite aggressive therapy, death is common within 7–10 days after onset of illness (100).

Similar clinical features are seen in Balamuthia infections and often mimic those of other encephalitides (106), with headache, fever, and nausea early and later development of seizures and cranial nerve palsies, making antemortem diagnosis difficult (106). The mortality rate is an extremely high 98% (109). Although no definitive therapy has been identified, seven survivors of infection with Balamuthia have been recorded: four survivors in the United States who were treated with a combination of pentamidine isethionate, fluconazole, flucytosine, sulfadiazine, and a macrolide antibiotic and three in Peru who were treated with albendazole and itraconazole (106,113).

Neuroimaging findings of granulomatous amebic encephalitis are nonspecific and may mimic those of a neoplasm or acute disseminated encephalomyelitis (Figs 14, 15) (109,113). Typical
Primary Amebic Meningoencephalitis

*Naegleria fowleri* (often called the “brain-eating ameba”) is a free-living thermophilic ameba that has a predilection for warm fresh water bodies (eg, lakes, rivers, and hot springs) and soil (115). Transmission to humans is believed to occur through the nasal cavity, and many cases are reported after a recent history of swimming or diving activities (115). Much less commonly, exposure to poorly chlorinated swimming pool water or heated and contaminated tap water has also been implicated. Drinking contaminated water is not linked to the disease (115).

*N fowleri* is the only species of *Naegleria* that is known to infect humans, causing primary amebic meningoencephalitis (115). In 1963, Malcolm foundings include hypoattenuation on CT images, hypointensity on T1-weighted MR images, and heterogeneous hyperintensity on T2-weighted MR images, with variable restricted diffusion and enhancement (109). The overall appearance is similar to that seen in other encephalitides, acute disseminated encephalomyelitis, neurocysticercosis, and toxoplasmosis (109). The appearance correlates with intense inflammation caused by trophozoites at histopathologic examination that leads to extensive necrosis and hemorrhage, findings frequently noted in postmortem whole brain sections (109). Ring-enhancing lesions in the brain have been reported in *Acanthamoeba* infections (114). Ranjan et al (100) described a case of *Acanthamoeba* infection in an interhemispheric ependymal cyst.

**Figure 15.** Granulomatous amebic encephalitis (due to *B mandrillaris*). (a) Axial T1-weighted MR image shows multifocal hypointense areas involving bilateral cerebral hemispheres (arrows), with mild hyperintensity in the right thalamus suggesting hemorrhage (arrowhead). (b) Axial T2-weighted FLAIR MR image reveals hyperintensity surrounding these areas (arrowheads), compatible with vasogenic edema. Smaller, more punctate hyperintensity in the left cerebral hemisphere suggests other areas of involvement. (c) Axial T2-weighted MR image reveals corresponding hyperintensity in these regions. (d) Axial contrast-enhanced T1-weighted MR image depicts only mild associated patchy enhancement. (e) Gross brain specimen shows extensive necrosis and hemorrhagic changes in the bilateral cerebral hemispheres, findings most prominent in the right thalamic region.
Figure 16. Primary amebic meningoencephalitis (due to N fowleri). (a) Axial contrast-enhanced T1-weighted MR image shows diffuse leptomeningeal enhancement (arrows). (b) Follow-up sagittal contrast-enhanced CT image reveals diffuse cerebellar hypoattenuation (arrowheads) related to edema and causing brainstem compression. (c) Gross brain specimen shows extensive hemorrhagic changes and necrosis in the bilateral cerebral hemispheres. (d) Gross brain specimen shows additional similar changes in the cerebellar hemispheres.

Fowler and Rodney Carter, two pathologists at Adelaide Children’s Hospital in Australia, described the first group of unusual extremely aggressive amebic infections resulting in death in four previously healthy children over a 4-year period. Although the cause was determined to be amebic meningoencephalitis, the ameba demonstrated histopathologic features that made it unique from Entamoeba histolytica (then recognized as the only common ameba to cause human infection) but otherwise defied classification. Postmortem examination of the brains showed a striking preponderance of amebic collections in the olfactory grooves and extensive destruction of the olfactory tracts but relative sparing of other areas of the brain, findings strongly suggesting that the ameba gained access to the intracranial compartment through the nasal cavity across the cribiform plate (116). In 1966, an American pathologist, Calvin Butt, described three cases of infection that were associated with swimming in warm lake water in Florida and that had similar pathologic features; he was the first to use the term primary amebic meningoencephalitis to describe the overall pathologic process (117). In distinction to granulomatous amebic encephalitis, primary amebic meningoencephalitis has no predilection for immunocompromised patients and routinely occurs in otherwise healthy children or young adults (115).

Although primary amebic meningoencephalitis predominates in warm weather, which is typical in the southern United States, the occurrence of the disease in a 7-year-old child in 2010 in Minnesota, 550 miles further north than the previously northernmost reported case in Missouri, proved that the organism can be found in water that is comparatively cooler (118). It is believed that humans are frequently exposed to N fowleri, but the occurrence of the disease is quite rare. The reason why some individuals experience full-blown infection and others never become infected is unknown.

Neuroimaging findings are nonspecific and may be normal early in the disease course. Later in the disease course, brain edema, leptomeningeal enhancement, and cerebral infarction (Fig 16) have been reported. It is suspected that the
Malaria

Malaria is regarded as the most important parasitic disease worldwide, with an estimated 300–500 million new cases and 1.5–2.7 million deaths annually. Although most of the fatal cases occur in sub-Saharan Africa, where the disease is endemic, 118 deaths were documented in the United States during 1979–1998 (120).

Malaria (from medieval Italian mala aria, meaning bad air) derives its name from swamp fumes and ancient miasma theory. The association between the cyclical febrile illness and stagnant water was explained in 1897 when Ronald Ross proved that malaria is transmitted by mosquitoes; he was awarded a Nobel Prize in 1902 for this discovery. Another Nobel Prize was awarded to Charles Louis Alphonse Laveran in 1907 for his earlier discovery of a protozoan parasite Plasmodium inside the red blood cells of infected patients in 1890. Infected erythrocytes are filled with multiplying merozoites; when the cell bursts, these merozoites infect other red blood cells, and other merozoites develop into gametocytes. These gametocytes mature in the gut of a fertilized Anopheles (from Greek an + ophelos, meaning useless) mosquito, which requires a blood meal to nourish her developing eggs. When the mosquito bites another host, mature sporozoites from the salivary glands enter the bloodstream and travel to hepatocytes, where they multiply into thousands of merozoites ready to parasitize the new host’s erythrocytes (121).

Plasmodium falciparum infection is the most deadly parasitic infection in the world, causing death in mostly young children in sub-Saharan Africa. Sequestration of infected erythrocytes in the microcirculation may lead to cerebral malaria (in 2% of cases), which manifests as encephalopathy or coma and is associated with a mortality rate of 15%–25% even when appropriate treatment is given (122). Antimalarial drugs include quinine, derived from cinchona bark, and artemisinin, derived from sweet wormwood. In serious cases, retinal whitening can be seen at fundoscopy and diffuse cerebral edema can be seen at neuroimaging; these findings are related to microvascular occlusion. A variety of MR imaging findings are reported in a small number of cases in the literature. Cortical infarcts and nonspecific white matter hyperintensity consistent with small-vessel ischemia have been seen at T2-weighted MR imaging (123). Additional involvement of the thalamus and basal ganglia is believed to represent the effects of encephalitis (124). One report noted that, at T2-weighted imaging, hyperintense lesions were more marked in the splenium of the corpus callosum (Fig 17) (125). Hemorrhagic infarctions may also occur (124,126). Petechial hemorrhages at the gray matter–white matter junction and in the deep white matter have been seen at gradient-recalled echo and susceptibility-weighted imaging (124,127,128).

Schistosomiasis

A major public health menace in developing countries, schistosomiasis is estimated to affect more than 200 million persons in Africa, Asia, and the Americas (129). Most human disease develops from infestation by one of three trematode worms—Schistosoma japonicum, Schistosoma mansoni, and Schistosoma hematobium—that live in certain freshwater snails (130,131), the larvae (cercariae) of which penetrate the skin in fresh water. The disease commonly manifests as dermatitis (“swimmer’s itch”) (130,131). After this acute phase, juvenile worms enter the circulatory system and adult female worms eventually develop in the urogenital and intestinal tracts. During this period, an acute reaction marked by fever, chills, sweating, and cough (“Katayama fever”) occasionally occurs (132). The final chronic organ-specific stage is related to the type of schistosome and is marked by a host immune response and granulomatous reaction (133). The introduction of praziquantel and albendazole as the primary therapeutic agents has been responsible for a substantial decrease in the prevalence of disease in many countries worldwide (131).

Most cases of cerebral schistosomiasis are caused by S japonicum, whereas spinal cord lesions are typically related to S mansoni and S hematobium (129,133). It is believed that the brain is involved through embolic distribution of the ova through venous shunts or by anomalous migration of adult worms, possibly through the vertebral venous (Batson) plexus (129,133–135). S mansoni, which is endemic in Brazil and is more notoriously noted for substantial hepatosplenic disease (splenomegaly, periportal fibrosis, portal hypertension, and upper gastrointestinal bleeding from esophageal varices), less commonly affects the brain (26% in one series) (129,136). Fever, focal neurologic deficits, and seizures are typical clinical symptoms of cerebral schistosomiasis (133).

Neuroimaging findings are variable and nonspecific. At CT, single or multiple variably enhancing hyperattenuated lesions with surrounding hypoattenuated edema may be present.
and reflect a focal granulomatous reaction in the cerebellum, cerebral hemispheres, thalamus, or dura (137). Findings in symptomatic patients frequently include masses with surrounding edema and nodular, ring, or patchy enhancement (133,137,138). Sanelli and colleagues (138) reported an “arborized” enhancement pattern with central linear enhancement that, when present, may be specific for schistosomiasis (Fig 18).

Spinal cord involvement from the disease shows hyperintensity at T2-weighted imaging and a similar enhancing pattern, usually in the distal thoracic spinal cord or cauda equina related to granulomatous involvement, presumably from extension through the vertebral venous (Batson) plexus (132,138,139). Acute or subacute transverse myelitis is common in this context, with typical early symptoms of back pain, urinary retention, and motor and sensory disturbances (132). Other myelopathic manifestations are related to spinal cord compression due to focal granulomas or anterior spinal artery syndrome (a rare complication) (139,140).

In addition to granulomatous lesions, findings related to a portosystemic shunt may be seen as bilateral symmetric hyperintensity of the globus pallidus at T1-weighted imaging, and substantia nigra in hepatic schistosomiasis japonicum (even in the absence of liver dysfunction) has been observed and is believed to be related to manganese deposition (129). Findings in children and young adults with hepatosplenic schistosomiasis mansoni commonly include cerebral white matter hyperintensity at T2-weighted imaging and symmetric basal ganglia hyperintensity with rare corpus callosum involvement at T1-weighted imaging (129).
Figure 18. Schistosomiasis. (a) Sagittal T1-weighted MR image shows a region of hypointensity (arrow) in the left parietal lobe. (b) Axial T2-weighted FLAIR MR image better depicts the nodular mass (arrow) with associated hyperintensity. (c) Coronal contrast-enhanced T1-weighted MR image shows an arborized pattern of enhancement (arrows), a finding reported to be specific to this disease.

Summary

Although the epidemiologic transition from infectious to degenerative disease has been completed in developed countries, the former remains an important source of morbidity and mortality worldwide, especially in less-developed countries and immunocompromised patients. Pyogenic bacteria cause acute meningitis, with streptococcal species being the most common. Imaging findings may be negative early or may include subtle signal abnormality in the cerebral sulci. Cerebritis is uncommon and, during a well-documented progression through four stages, encapsulates into an abscess over 2–4 weeks. Pus shows restricted diffusion from high cellularity and viscosity. Pyogenic abscesses often show amino acids at spectroscopy that result from neutrophils and proteolytic enzymes.

Atypical bacteria evade neutrophils through various methods, and granulomatous inflammation develops. Neutrotuberculosis and neurosyphilis manifest as nodular meningeal enhancement and/or vasculitis, which can also be seen with fungal infections. Neuroborreliosis manifests as leptomeningeal enhancement and white matter lesions. Rickettsiae cause meningitis with diffuse systemic small-vessel thrombovasculitis.

Many of the neuromycoses, including the yeast Cryptococcus and the dimorphic fungi Coccidioides, Histoplasma, and Blastomyces, begin with spore inhalation, followed by hematogenous dissemination in susceptible individuals. Imaging manifestations may resemble those of other granulomatous diseases, such as tuberculosis. Gelatinous pseudocysts are seen in cryptococcal disease. Immunodeficient patients are at risk for parenchymal disease in the context of aspergillosis and mucormycosis due to filamentous fungi, whereas microabscesses are seen in invasive candidiasis due to pseudohyphae.

Parasites can be unicellular (protozoa) or multicellular (helminths) with complex life cycles involving intermediate and definitive hosts. Although progress has been made in containing some of these infections, they remain a significant health risk for hundreds of millions of individuals in certain regions of the world. A select few of these infections are noteworthy for their devastating virulence, even in immunocompetent hosts, and for causing unexpected rapid death.

From an imaging perspective, it is important to recognize the limitations of early imaging and overlapping imaging appearances for many of these diseases. Some diseases, such as neurocysticercosis and echinococcosis, may have highly characteristic patterns of CNS involvement; however, many other infections share common imaging findings and a high degree of suspicion is required to initiate confirmation of the disease with additional laboratory examination, particularly CSF analysis.

Acknowledgments.—The authors gratefully acknowledge the contributions of case material to the American Institute for Radiologic Pathology and Armed Forces Institute of Pathology from radiology residents worldwide.
References


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