Imaging of Rickettsial, Spirochetal, and Parasitic Infections

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KEY POINTS

- Rickettsial, spirochetal and parasitic central nervous system (CNS) infections, although generally quite rare, are still being encountered in endemic regions around the world.
- Toxoplasmosis and neurosyphilis may manifest as opportunistic infections in immunocompromised patients, particularly in patients infected with human immunodeficiency virus.
- CNS involvement in spirochetal infections, particularly in neurosyphilis and Lyme disease, is quite varied in clinical presentation and imaging findings.
- A high index of suspicion and knowledge of the imaging features may lead to early diagnosis of the rickettsial, spirochetal, and parasitic CNS infections.

RICKETTSIAE

The Rickettsiae are small gram-negative bacteria, which are generally obligate intracellular parasites and transmitted to humans by arthropods.[1] The exception is Coxiella burnetii, which is transmitted by inhalation and has an endospore form that is capable of surviving in an extracellular environment.[2,3] The most common rickettsial infections are Rocky Mountain spotted fever, epidemic typhus, and Q fever. Rickettsial infections except for Q fever typically present with fever, rashes, and vasculitis. Imaging findings of central nervous system (CNS) involvement in Rocky Mountain spotted fever reported to date include diffuse cerebral edema, meningeal enhancement, arterial infarction, and signal abnormality within the distribution of perivascular spaces, which are dissimilar to the documented neuroimaging findings of Q fever consisting of (meningo) encephalitis, acute cerebellitis, and transverse myelitis.[4–9] To the authors' knowledge, there are no existing reports documenting neuroimaging findings of epidemic typhus or more commonly referred to as simply typhus. It should not be confused with typhoid fever, also known as typhoid, caused by the bacterium Salmonella typhi.

Owing to the small size of the bacteria, direct microscopic visualization of Rickettsiae is difficult and requires special stains such as Giemsa or Gimenez. Hence, serologic tests such as complement fixation test, indirect immunofluorescence, latex agglutination, and enzyme immunoassay tests, are commercially available and are used in the diagnosis of Rickettsial disease. Tetracyclines and chloramphenicol are effective in treatment, whereas sulfonamides enhance the disease and are contraindicated.

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Rocky Mountain Spotted Fever

The causative agent in Rocky Mountain spotted fever is Rickettsia rickettsii, which is transferred to humans by the dog or wood tick bite. As opposed to the name that implies a mountainous predisposition, approximately 25% of the cases occur in North Carolina and more than 50% of the cases were reported in the South Atlantic region of the United States.[4,10] Rickettsia rickettsii spreads via the blood stream, proliferates, and injures endothelial and vascular smooth muscle cells, thereby causing damage to the microcirculation of virtually all organs.[5] Vascular lesions are prominent in the skin explaining the pathophysiologic basis for the rash found in Rocky Mountain spotted fever.[2,5] The skin rash initially appears on the wrists, ankles, soles, and palms and later spreads to the trunk.[3] The maculopapular skin lesions, later in the disease, may become petechial and eventually purpuric and ecchymotic and can rarely lead to skin necrosis or gangrene.[5] Other clinical manifestations include fever, headache, myalgias, confusion, meningismus, ataxia, aphasia, paralysis, seizures, and coma.[10] In the brain, vasculitis forms a characteristic pathologic appearance called typhus nodules, which are essentially perivascular infiltrates of lymphocytes, polymorphonuclear leukocytes, and macrophages.[2,5] Other pathologic lesions include white matter microinfarctions and a predominantly mononuclear cell leptomeningitis. Early recognition of the CNS involvement is critical, because such involvement often causes increased mortality.[5] Rocky Mountain spotted fever is still the most frequently reported life-threatening tick-borne infection, with mortality rates ranging from 2% to 10% even under adequate antibiotic therapy.[4,11] The largest case series reported in the literature was contributed by Bonawitz and colleagues[4] and reported the associated neuroimaging findings in patients with Rocky Mountain spotted fever. Of 34 patients, 28 had computed tomography (CT) of the brain (44 studies, 10 after contrast administration), 6 had contrast-enhanced brain magnetic resonance (MR) imaging, and 4 had both CT and MR studies of the brain. Four patients demonstrated abnormalities on CT imaging, including focal arterial basal ganglia infarction, diffuse cerebral edema, and diffuse meningeal enhancement (**Fig. 1**). MR imaging was abnormal in 4 patients with findings consisting of focal basal ganglia and frontal lobe arterial infarctions, diffuse edema, diffuse meningeal enhancement, and prominent perivascular spaces in the region of the basal ganglia. In addition, one patient had thoracolumbar contrast-enhanced spine MR imaging, which depicted abnormal enhancement along the surfaces
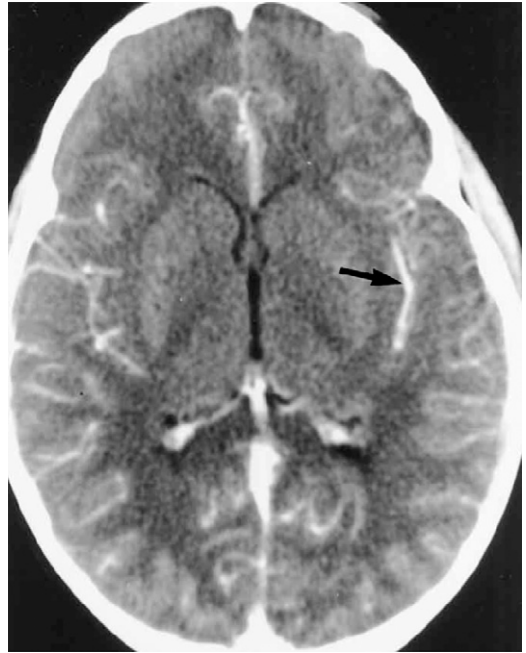

Fig. 1. Rocky Mountain spotted fever. Meningeal enhancement on CT. Axial post-contrast CT sections show enhancement of the subarachnoid space in both cerebral hemispheres, particularly at the level of the left Sylvian fissure (*arrow*). However, some of the enhancement may represent prominent vessels. At presentation, this patient was posturing and unresponsive and died during hospitalization. Autopsy showed meningitis with swollen and congested vessels in the leptomeninges and neuronal necrosis in the hippocampi. (*From* Bonawitz C, Castillo M, Mukherji SK. Comparison of CT and MR features with clinical outcome in patients with Rocky Mountain spotted fever. AJNR Am J Neuroradiol 1997;18(3):459–64; with permission.)

of the distal spinal cord as well as enhancement of the cauda equina (**Fig. 2**). Although the presence of abnormal neuroimaging is rare, its presence is associated with worse clinical prognosis. However, the neuroimaging findings are potentially reversible if appropriate treatment is initiated early in the course of the disease. Total resolution of MR imaging findings was also shown in a single case by Baganz and colleagues[5] in which there was reversal of extensive T2 signal abnormality in the distribution of the perivascular spaces without accompanying abnormal enhancement. Although nonspecific and also reported in diseases such as cryptococcosis and Lyme disease, the investigators postulated perivascular signal abnormality may reflect the underlying pathophysiology of Rocky Mountain spotted fever (**Fig. 3**).
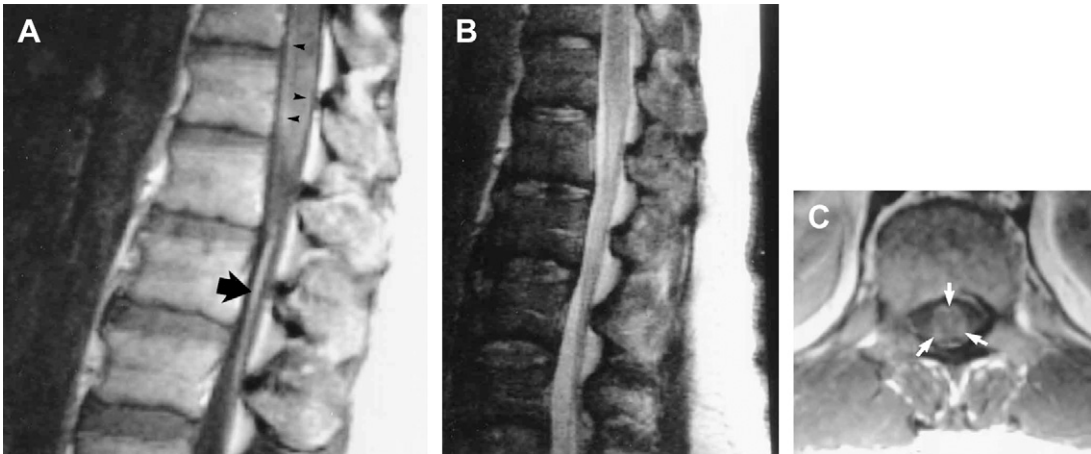
Fig. 2. Rocky Mountain spotted fever. Abnormal enhancement of the distal spinal cord, conus medullaris, and cauda equina. (*A*) Midsagittal T1-weighted MR image after contrast administration shows enhancement of the ventral and dorsal surface of the conus medullaris (*arrowheads*) and of the cauda equina (*arrow*). This patient presented with mental status changes, ataxia, aphasia, and bilateral lower extremity weakness. Residual parapa-resis remained after treatment. (*B*) Corresponding T2-weighted MR image shows a questionable area of abnor-mally high signal intensity in the distal conus medullaris at the level of L-1. (*C*) Axial post-contrast T1-weighted MR image shows abnormal enhancement (*arrows*) on the surface of the distal thoracic spinal cord. Analysis of cerebrospinal fluid showed lymphocytosis and elevated proteins. Two years after presentation, the patient has mild residual bilateral lower extremity weakness. (*From* Bonawitz C, Castillo M, Mukherji SK. Comparison of CT and MR features with clinical outcome in patients with Rocky Mountain spotted fever. AJNR Am J Neuroradiol 1997;18(3):459–64; with permission.)
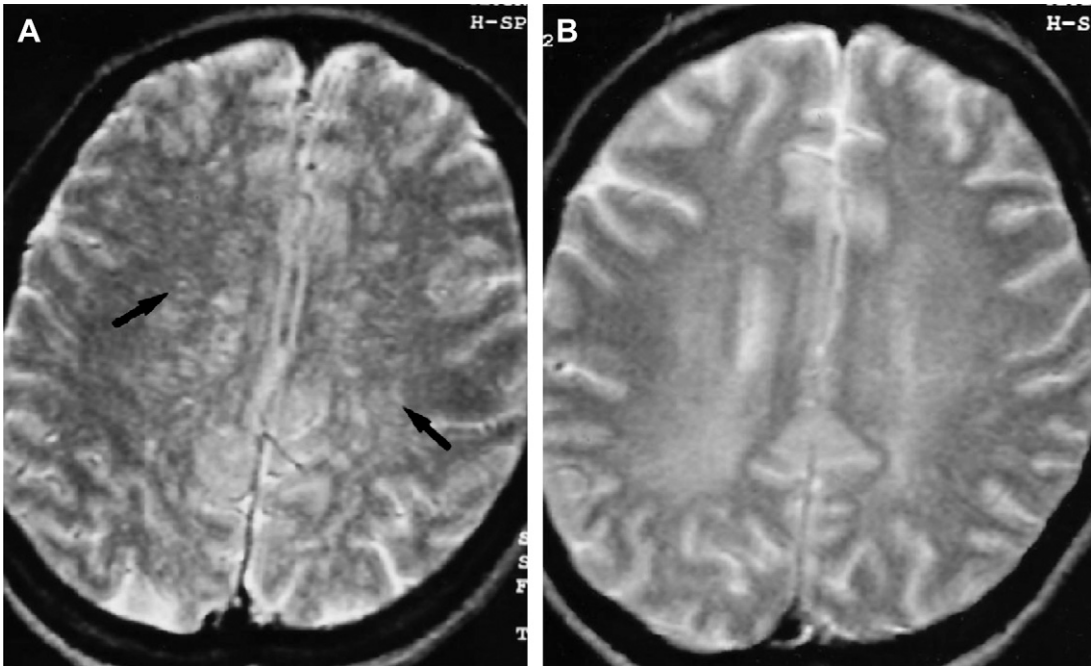

Fig. 3. Rocky Mountain spotted fever. (*A*) T2-weighted MR images (2000/80/2 [repetition time/echo time/excita-tions]) of the brain obtained at admission show numerous punctate regions of increased signal (*arrows*) in the distribution of perivascular (Virchow-Robin) spaces. (*B*) T2-weighted MR images (2000/80/2) of the brain obtained after clinical improvement show substantial resolution of the high signal, corresponding to resolution of the peri-vascular inflammation. (*From* Baganz MD, Dross PE, Reinhardt JA. Rocky Mountain spotted fever encephalitis: MR findings. AJNR Am J Neuroradiol 1995;16(Suppl 4):919–22; with permission.)

Epidemic Typhus

The causative agent of epidemic typhus is Rickettsia prowazekii, which is transmitted to humans via the louse. Similar to Rocky Mountain spotted fever, Rickettsia prowazekii has tropism to endothelial cells inducing clotting, which can lead to gangrene of the hands and feet.[3] The disease is characterized by fever, headache, and a rash sparing the palms, soles, and face. This disease is typically seen in an epidemic setting especially in overcrowded populations living in poverty and unsanitary conditions. The disease is still considered to be a major threat by public health authorities, despite the efficacy of antibiotics, because poor sanitary conditions are conducive to louse proliferation. Previously Rickettsia prowazekii, the causal agent, was thought to be confined to human beings and their body lice; however, in 1975, Rickettsia prowazekii infection in human beings was observed due to contact with the flying squirrel Glaucomys volans in the United States.[12]

Q Fever

This disease is recognized around the world and occurs mainly in people who come into contact with goats, sheep, and dairy cattle.[2] Coxiella burnetii, the organism of Q fever, possesses unique characteristics within the Rickettsiae family such as the ability to form an endospore that is resistant to heating and drying and does not need a vector to be transmitted to humans.[10] Transmission results from inhalation of dust contaminated with Coxiella burnetii from placenta, dried feces, urine, or milk or from aerosols in slaughterhouses.[2] This disease resembles influenza, nonbacterial pneumonia, endocarditis, hepatitis, and encephalopathy rather than typhus. CNS involvement is a rare manifestation documented in a few reports of (meningo) encephalitis that occurred in the late course of acute Q fever.[8] Sawaishi and colleagues[6] reported an 8-year-old child presenting with a 1-week history of moderate fever and headache and found to have acute cerebellitis on MR imaging with swelling and diffuse T2 signal abnormality of a cerebellar hemisphere. Serologic tests revealed positive titers for Q fever. The acute imaging findings resolved following treatment with only residual parenchymal volume loss of the affected cerebellar hemisphere. Sempere and colleagues[7] documented a case of Q fever encephalitis involving the temporal lobe, which created confusion at initial presentation with resemblance to herpes simplex encephalitis. In addition, there are a few reports in the literature concluding that infection with Coxiella burnetii can be associated with acute transverse myelitis as a result of direct infectious or parainfectious pathogenic mechanisms.[8,9] This central nervous manifestation of Coxiella burnetii adds to the treatable causes of acute myelitis and should therefore be considered as a differential diagnosis, especially in areas endemic for Q fever. Moreover, in a study by Garron and colleagues,[13] Coxiella burnetii was amongst the causative agents for nontuberculous spondylodiscitis in children in whom MR imaging and needle aspiration of the disc aided in diagnosis.

SPIROCHETES

Spirochetes are a phylum of gram-negative bacteria, which are distinguished by the location of their flagella that run lengthwise between the cell wall and outer membrane. These flagella cause a spiral motion that facilitates movement. Three genera whose members are human pathogens are Treponema, Borrelia, and Leptospira.[2] Syphilis and Lyme disease, which are caused by Treponema pallidum and Borrelia burgdorferi, respectively, are the most commonly encountered diseases in this pathogen group. Both diseases present in the form of well-recognizable clinical stages usually beginning with an initial skin lesion. However, CNS involvement in both diseases is quite varied in clinical presentation and imaging findings. In addition, imaging may be normal in both diseases even in the setting of known CNS involvement with evidence of positive cerebral spinal fluid (CSF) tests. Neurosyphilis may present with numerous findings including: meningeal and cranial nerve enhancement, arteritis and ischemia, mass lesions known as gummas, cortical atrophy, hydrocephalus, and mesial temporal signal abnormality mimicking herpes simplex encephalitis, mesial temporal sclerosis, and paraneoplastic limbic encephalitis. Hence, it is called "the great imitator".[14–26] Similarly, Lyme disease also acts as an imitator with various clinical and radiologic presentations. Imaging findings of CNS involvement of Lyme disease are also myriad including, meningeal and cranial nerve enhancement, white matter signal abnormality occasionally resembling multiple sclerosis, prominent Virchow-Robin spaces, enhancing masslike parenchymal lesions, arteritis, ischemia, hemorrhage, meningoradiculitis, acute transverse myelitis, and ocular myositis.[14,27–52]

Syphilis

Syphilis is a chronic venereal disease with multiple presentations. The causative spirochete, Treponema pallidum is a gram-negative corkscrew-shaped bacterium, which is too slender to be seen on Gram stain, but can be visualized by silver

stains, dark-field examination, and immunofluorescence techniques.[53] Sexual contact is the usual mode of spread. However, there may be nonsexual transmission via skin contact with an infected skin ulcer. Transplacental transmission of Treponema pallidum occurs readily, and active disease during pregnancy results in congenital syphilis.

Syphilis is a chronic infection with 3 well-characterized stages. Cases of syphilis surged upward in the setting of AIDS.[14] Primary syphilis is characterized by a chancre (sore or ulcer) at the site of inoculation and painless regional lymphadenopathy. If left untreated, a secondary stage manifests during which a maculopapular rash is seen on the palms of the hand and soles of the feet with hematological dissemination of the bacteria. This rash is usually seen 2 to 8 weeks after the chancre appears, but in AIDS patients, there is much more rapid progression to secondary syphilis. About one-third of patients with secondary syphilis progress to tertiary syphilis and approximately one-third of those develop neurosyphilis. The tertiary stage usually occurs after a latent period of at least 5 years and has 3 main manifestations: cardiovascular syphilis, neurosyphilis, and syphilitic gummas. Cardiovascular disease is usually in the form of luetic aortitis which becomes apparent as aortic valve insufficiency and aneurysms of the proximal aorta. Gummas are nodular lesions likely related to the development of delayed hypersensitivity to the bacteria. These lesions may occur in various sites, most commonly in bone, skin, and the mucous membranes of the upper airway and mouth.[53]

Although neurosyphilis may appear at any stage of systemic infection, more commonly it occurs at late stages, primarily the tertiary stage.[14] CNS involvement can be asymptomatic, which accounts for about one-third of neurosyphilis cases and detected when CSF tests are abnormal with increased white cell counts, especially lymphocytes, increased protein, and decreased glucose.[53] Although symptomatic neurosyphilis may manifest in several ways, in general, 2 major clinical subtypes are recognized: (1) meningovascular disease and (2) parenchymal disease.[14]

Meningeal neurosyphilis usually appears within the first 2 years of infection and may result in headache, meningeal signs, and cranial nerve palsies, most frequently involving cranial nerves VII and VIII (**Fig. 4**). Pathologically, there is widespread thickening of the meninges, meningeal lymphocytic infiltrates, and perivascular lymphocytic infiltrates. Meningeal enhancement may be present and is usually better seen on MR imaging than CT.[14] Hydrocephalus may also occur. Involvement of cranial nerves VII and VIII in syphilitic basilar
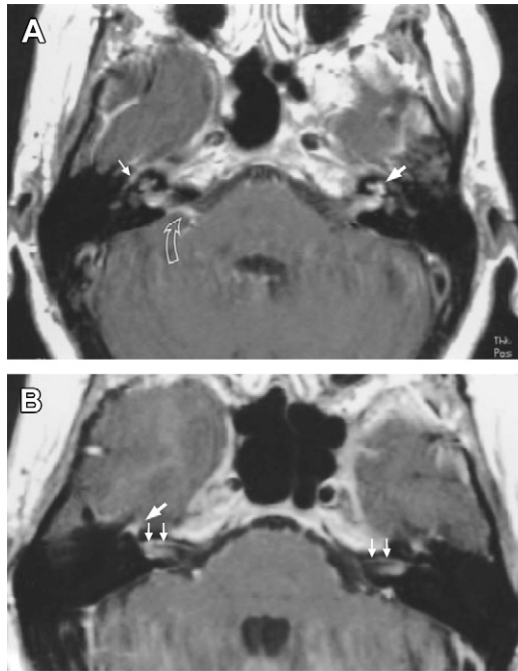

Fig. 4. Neurosyphilis. (*A*) Axial T1-weighted MR image (450/15/4), obtained after the administration of contrast medium, shows enhancement within the cisternal segment of the vestibulocochlear nerve complex on the right (*curved open arrow*), within both internal auditory canals, within the left cochlea (*curved solid arrow*), and within the tympanic portion of the right facial nerve (*small arrow*). The enhancement within the internal auditory canals involves both the nerves within the CSF and the meninges lining the canal. Enhancement is also seen within the middle turn of the right cochlea. (*B*) Axial T1-weighted MR image (450/15/4), obtained after the administration of contrast medium from a position that is slightly superior to that of **Fig. 4** (*A*), shows enhancement of the labyrinthine and geniculate portions of the right facial nerve (*large arrow*) and enhancement of the meninges lining both internal auditory canals (*small arrows*). Enhancement of the intracanalicular segments of the seventh and eighth cranial nerve complex is appreciated bilaterally. (*From* Smith MM, Anderson JC. Neurosyphilis as a cause of facial and vestibulocochlear nerve dysfunction: MR imaging features. AJNR Am J Neuroradiol 2000;21(9):1673–5; with permission.)

meningitis presents with facial paralysis, sensorineural hearing loss, and vertigo and radiologically, with enhancement of the seventh and eighth cranial nerves and cochlea as well as the meninges lining the internal auditory canals.[15] Involvement of the optic, oculomotor, and abducens nerves has also been reported (**Fig. 5**).[16,54]

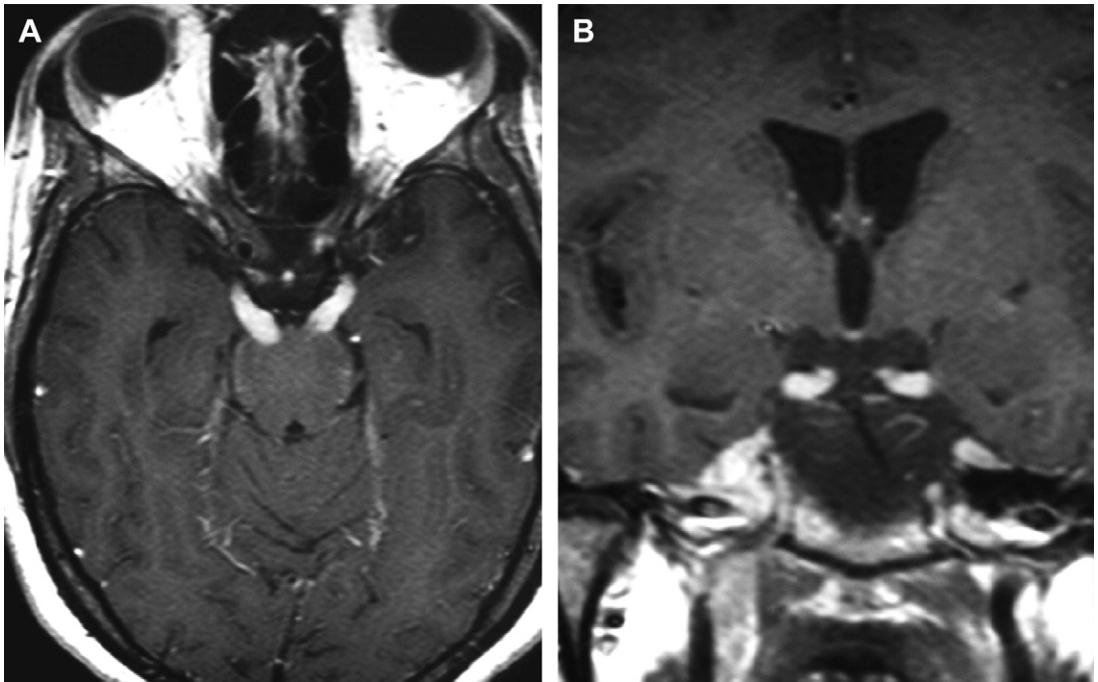Syphilitic gummas are another manifestation of meningovascular neurosyphilis and occur as the

Fig. 5. Neurosyphilis. Contrast-enhanced T1-weighted (*A*) axial and coronal MR images (*B*) through the brainstem and proximal oculomotor nerves demonstrate bilateral thickening and contrast enhancement. (*From* Corr P, Bhigjee A, Lockhat F. Oculomotor nerve root enhancement in meningovascular syphilis. Clin Radiol 2004;59(3): 294–6; with permission.)

result of intense localized leptomeningeal inflammatory reaction early in the meningeal phase of neurosyphilis.[14] Pathologically, gummas appear as circumscribed masses of granulation tissue surrounded by mononuclear epithelial and fibroblastic cells with occasional giant cells and perivasculitis. They originate from the meningeal connective tissue and blood vessels extending to the adjacent parenchyma and leading to meningeal enhancement.[14] On imaging, gummas are seen as circumscribed solitary or multiple mass lesions with nodular or ring enhancement usually located overlying the cerebral convexities. However, they can be found anywhere in brain parenchyma that is adherent to dura. There may be an associated dural tail (**Fig. 6**).[55] Whereas cutaneous, mucosal, and skeletal gummatous lesions are not uncommon, neurosyphilitic gummas are rare.[56] The imaging findings of cerebral gumma may mimic those of other intracranial mass lesions, especially brain neoplasms, and definitive diagnosis has always been difficult (**Fig. 7**).[17–19] Moreover, gummas may demonstrate intense ^{18}F-2-fluoro-2-deoxy-D-glucose (FDG) avidity on positron emission tomography (PET)
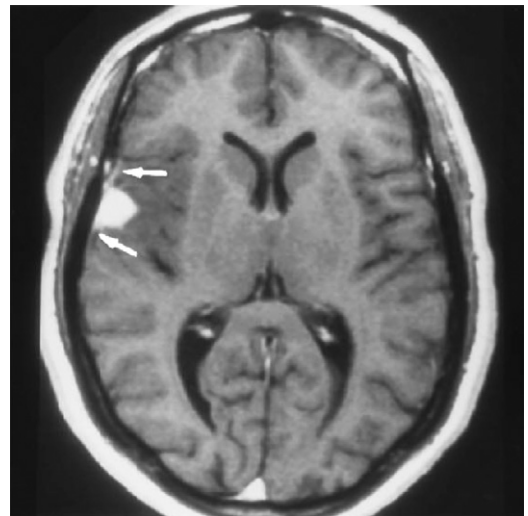

Fig. 6. Neurosyphilis. Enhanced axial T1-weighted (576/14/2) image shows intense enhancement of a 1.3-cm mass in the region of the right sylvian fissure, with enhancement of the adjacent dura (*arrows*). This is surgically proved syphilitic gumma. (*From* Bourekas EC, et al. The dural tail sign revisited. AJNR Am J Neuroradiol 1995;16(7):1514–6; with permission.)
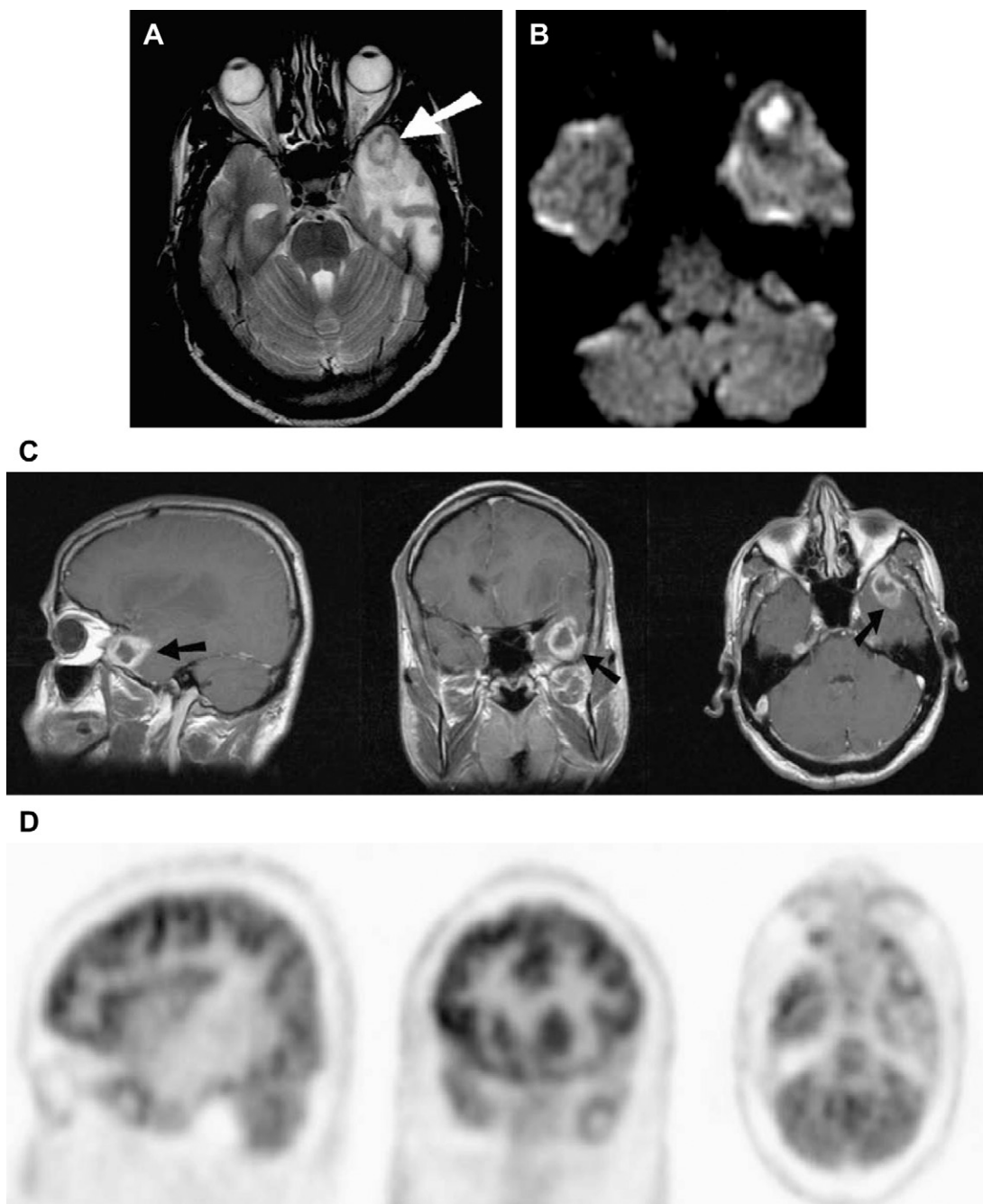
Fig. 7. Neurosyphilis. Neurosyphilitic gumma. (*A*) An axial T2-weighted MR image of the brain (Siemens Symphony 1.5T, Siemens Medical Systems, Erlangen, Germany) demonstrated edema in the left temporal lobe surrounding the lesion, which has a hypointense rim (*arrow*). (*B*) Diffusion-weighted axial MR image revealed restricted diffusion centrally within the lesion. The overall MR imaging appearances are suggestive of an abscess or a high-grade primary brain tumor such as glioblastoma multiforme with tumor necrosis. (*C*) The T1-weighted gadolinium-enhanced MR imaging in the sagittal (*left*), coronal (*middle*), and axial (*right*) planes showed an irregular ovoid lesion with a thick enhancing rim (*arrows*) and a hypointense center in the left temporal lobe associated with a significant midline shift and edema. There was also effacement of the left frontal horn of the lateral ventricle. (*D*) An ¹⁸F-FDG PET of the brain using a Philips Allegro PET camera (Philips Medical systems, Milpitas, CA, USA) demonstrated an intensely FDG avid lesion at a metabolic activity similar to contralateral cortex, with a small central photon-deficient area, corresponding to the abnormality seen on MR imaging. There was also surrounding diffuse, mild-to-moderately reduced FDG uptake in the remainder of the left temporal lobe in keeping with associated edema. The overall appearances are suspicious for high-grade malignancy. ([D] *From* Lin M, Darwish BS, Chu J. Neurosyphilitic gumma on F18-2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography: an old disease investigated with a new technology. J Clin Neurosci 2009;16(3):410–2; with permission.)

as is seen with hypermetabolic tumors and this further poses challenges to diagnostic imaging (**Fig. 7**D).[56] A high index of suspicion and knowledge of the imaging features may lead to early diagnosis of this lesion, which is important because these lesions may regress or even disappear following penicillin treatment.[17]

Vascular neurosyphilis usually appears around 5 to 10 years after primary infection and is typically characterized by headache, vertigo, and focal neurologic deficit related to a vascular event, with abnormal CSF findings.[14] Two types of vascular involvement have been described in neurosyphilis: Heubner endarteritis and Nissl-Alzheimer endarteritis.[10] Heubner arteritis, the most common form of syphilitic arteritis, affects large- and medium-sized arteries and is characterized by fibroblastic proliferation of the intima, thinning of the media, and adventitial fibrous and inflammatory changes, resulting in an irregular luminal narrowing and ectasia. Nissl-Alzheimer type of arteritis typically affects small vessels and manifests as thickening of the adventitia to a greater degree than the endothelium. Both types of arteritis may lead to vascular occlusion.[14] The most common clinical presentation is an ischemic syndrome in a young adult, involving the middle cerebral artery or less commonly the branches of the basilar artery.[20,57] Although the causes of vasculitis are relatively extensive, including infectious agents (eg, tuberculosis, syphilis, fungal disease), collagen vascular diseases, Takayasu arteritis, sarcoidosis, and drug-related and radiation-induced conditions, imaging findings of arteritis on MR imaging and magnetic resonance angiography in young adults with symptoms of ischemic stroke should serve as an indicator for meningovascular syphilis, particularly in an immunocompromised host prone to opportunistic infection.[16,20]

General paresis is a form of chronic meningoencephalitis and usually presents 10 to 20 years after the initial infection.[14] It is a manifestation of diffuse parenchymal damage and may result in modifications of personality and affect, delusions, hallucinations, memory loss, loss of judgment and insight associated with speech disturbances, hyperactive reflexes, and the Argyll Robertson pupil. Argyll Robertson pupil, which is seen in both tabes dorsalis and general paresis, is a small irregular pupil that accommodates but does not react to light.[14] Neuropathologically, cortical atrophy and ependymitis are observed on gross examination associated with degenerative neuronal changes with gliosis and scattered microglia. Cortical atrophy is seen on MR imaging. There is often an associated hydrocephalus with damage to the ependymal lining and proliferation of subependymal glia called granular

ependymitis.[53] The hydrocephalus in association with impaired memory may occasionally mimic normal pressure hydrocephalus.[21] There are a few recent reports in the literature demonstrating unilateral or bilateral anterior temporal and mesiotemporal signal abnormality in patients with serologic or CSF evidence of neurosyphilis with or without accompanying abnormal enhancement mimicking mesial temporal sclerosis, herpes encephalitis, and paraneoplastic limbic encephalitis.[21–26] Partial clinical or radiologic improvement has been shown with penicillin treatment in some patients.

Tabes dorsalis is a myelopathy caused by the damage to the sensory nerves in the dorsal roots and posterior spinal columns associated with atrophy, degeneration, and demyelination.[14,53] A latent period of 15 to 20 years is usually seen with clinical tabes dorsalis, characterized classically by lightning pains, dysuria, ataxia, Argyll Robertson pupil, areflexia, and loss of proprioception.[16]

Lyme Disease

Lyme borreliosis is a multisystemic infectious disease caused by the spirochete Borrelia burgdorferi sensu stricto in the United States and Borrelia garinii and Borrelia afzelii in Europe, which is transmitted to humans by the bite of infected Ixodes ticks.[27] Lyme disease is named for the Connecticut town where there was an epidemic of arthritis associated with skin erythema in 1976.[53] It is a worldwide common arthropod-borne disease, particularly in the United States, Europe, and Japan and currently the most common vector-borne disease in the United States with a national incidence of 9.7 cases per 100,000.[27] Most cases occur in the coastal Northeast states (from Massachusetts to Maryland), the Midwest (Minnesota and Wisconsin), and the West (California, Oregon, Utah, and Nevada).[28] Most of the Lyme disease exposures are in May through July when the nymphal stage of the ticks is most active, which primarily transmits Borrelia burgdorferi to human beings.[2]

Similar to other spirochetal diseases such as syphilis, Lyme disease is clinically encountered in 3 main stages classified as early localized disease, early disseminated disease, and persisting late disease.[58] During the initial stage, spirochetes multiply in the dermis at the site of the tick bite and later spread centrifugally, which may result in an area of enlarging erythema, often associated with central clearing that resembles a bull's eye appearance.[53,58] This characteristic skin lesion is called erythema chronicum migrans and may be accompanied by flu-like symptoms and lymphadenopathy and usually disappears in 4 to

12 weeks. In the second stage, the early disseminated stage, spirochetes spread throughout the body via the blood stream, which may cause diverse clinical presentations, including arthralgia, arthritis, lymphocytic meningitis, cranial neuropathy most commonly Bell palsy, painful radiculopathy; and cardiac disease with conduction defects and myopericarditis.[2] If left untreated, a late disseminated stage may be seen generally 2 or 3 years after the initial bite, with a chronic arthritis sometimes with severe damage to large joints and a polyneuropathy and encephalitis that may vary from mild to debilitating.

The diagnosis of Lyme disease is essentially clinical based on a history of tick exposure, epidemiology, and clinical signs and symptoms at different stages of the disease, usually with use of serologic tests supporting the clinical diagnosis. Current standards for the serologic diagnosis of Lyme disease include a sensitive enzyme immunoassay (EIA), followed by confirmation of a positive or equivocal initial test by Western blot or immunoblot as Borrelia burgdorferi has extremely complex antigenic composition that may vary by host and stage of the infection.[27]

CNS symptoms are seen in about 15% to 20% of patients with the characteristic initial skin lesion.[14] However, CNS disease may occur without a preceding erythema chronicum migrans or may manifest as an isolated neurologic syndrome, which may pose a diagnostic challenge for practicing neurologists.[14] The genetic diversity and worldwide differential distribution of spirochete species affect the seasonal incidence and disease manifestations as well as the likelihood of a patient developing Lyme neuroborreliosis (LNB).[27,29] For instance, LNB is much more frequently seen in Europe in comparison to North America, which could be linked to probable greater neurotropism of Borrelia garinii, which has not been isolated in North America.[58] In addition, 86% of European LNB present as a painful radiculitis, which was first reported by Garin and Bujadoux in 1922 and is also known as Bannwarth syndrome.[30,59] The pain associated with Bannwarth syndrome is mostly described as a chronic pain lasting weeks or months, which can occasionally be severe and may increase in intensity at night. Moreover, lack of a recognizable erythema migrans is more frequently seen in Europe, which makes the diagnosis of LNB much more difficult.[27]

Despite increased knowledge and experience in diagnosis and treatment of LNB in common daily clinical neurologic practice, the underlying neuropathophysiology is still unclear. Several proposed mechanisms for CNS injury include direct cytotoxicity, neurotoxic mediators secreted by leukocytes and glial cells (indirect cytotoxicity), or triggered autoimmune reactions via molecular mimicry.[61] It is also a matter of debate how spirochetes reach the CNS and pass the blood-brain barrier. Given cultivation of Borrelia from plasma samples in approximately 35% to 45% of patients with early Lyme disease in the United States, hematogeneous dissemination of the spirochetes is considered frequent in patients with Lyme disease in the United States.[61] In contrast, it is hypothesized that migration of the spirochetes along the peripheral nerves is an alternative route to the CNS, particularly in European LNB. The initial and maximal radicular involvement in patients with meningoradiculitis (Bannwarth syndrome) is often linked to the location of the previous tick bite or the skin lesion.[61] Studies involving the nervous system in rhesus macaques localized LNB-associated inflammation within dorsal root ganglia, nerve roots, and leptomeninges with predominance of T-lymphocytes and plasma cells.[60] In addition, visualization of the spirochetes by immunohistochemistry in the leptomeninges, nerve roots, and dorsal root ganglia, but not in the CNS parenchyma, is consistent with the commonly encountered pattern of clinical involvement in infected human beings, with predominance of meningitis, radiculitis, and cranial nerve involvement, and, rarely, parenchymal brain and spinal cord involvement. On the other hand, there are a few case reports in the literature with presentation of findings from biopsy of tumefactive parenchymal lesions in patients with LNB with presence of a small number of spirochetes accompanied by microgliosis in 1 patient and presence of Borrelia burgdorferi DNA in tissue samples in 2 patients, which may indicate that direct invasion of Borrelia burgdorferi may be the pathogenetic mechanism for focal encephalitis in LNB.[31,62] Oksi and colleagues[31] detected perivascular or vasculitis lymphocytic inflammation in all 3 biopsy specimens suggestive of probable role of vasculitis in the pathogenesis of Lyme neuroborreliosis.

MR imaging findings of the brain in Lyme disease are often within normal limits, even in patients with known Lyme disease who have neurologic manifestations.[14,28] There are several studies in the literature that have evaluated MR neuroimaging findings in patients with Lyme disease and identified multiple bilateral periventricular and/or subcortical foci of T2 prolongation in patients with neurologic symptoms.[32,63–67] Some of the lesions are said to resemble multiple sclerosis plaques with involvement of the callososeptal interface (Fig. 8).[31,33] Although similar mechanisms of molecular mimicry and antigen-specific T-cell response have been identified in both multiple sclerosis and chronic LNB, T-cell
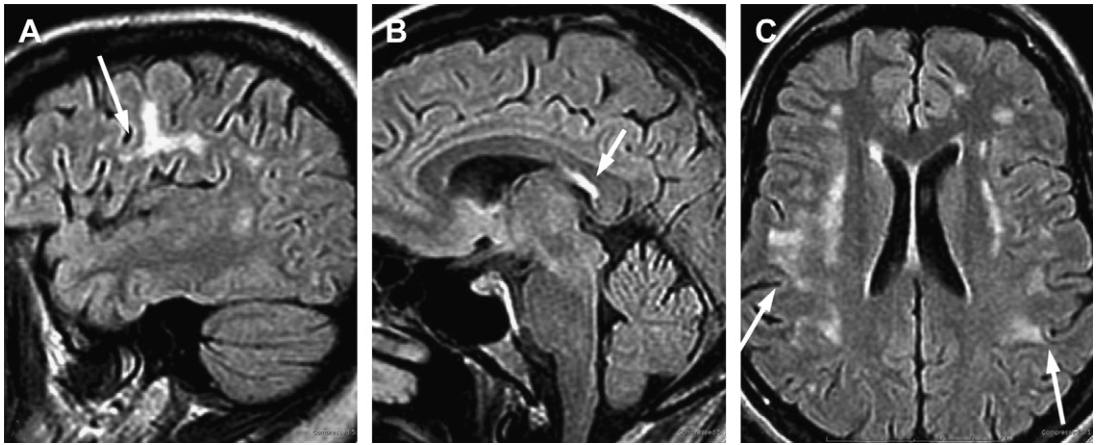
Fig. 8. Lyme disease. A 50-year-old woman with a history of tick bite and erythema migrans rash treated with doxycycline, who had recurrent erythema migrans rash with headache, fever, nausea, and nuchal rigidity. The patient had CSF pleocytosis with positive Lyme serum EIA and immunoglobulin M Western blot and negative Lyme antibodies in the CSF. Gradual symptomatic improvement occurred after intravenous ceftriaxone therapy. There has been stable MR imaging for 5 years. Sagittal (*A* and *B*) and axial (*C*) fluid-attenuated inversion recovery images show arcuate and confluent subcortical white-matter involvement and callososeptal interface involvement remarkably similar to that in multiple sclerosis, but without involvement of the periventricular white matter (*arrows*). (*From* Hildenbrand P, et al. Lyme neuroborreliosis: manifestations of a rapidly emerging zoonosis. AJNR Am J Neuroradiol 2009;30(6):1079–87; with permission.)

lines demonstrate only weak cross reactivity between myelin basic protein and Borrelia burgdorferi.[27] I addition, studies using diffusion tensor and magnetization transfer imaging demonstrated that contrary to what happens in multiple sclerosis, occult brain tissue damage and cervical cord pathology are not frequent findings in patients with neuroborreliosis.[67] Basal ganglia and the brainstem may also be involved.[14,32,34] Accompanying multifocal parenchymal enhancement has also been described.[35] Rare cases of parenchymal brain involvement have been reported, often either misdiagnosed initially as brain tumors or thought to represent encephalitis.[31,36,37] Recently, Agarwal and Sze[28] have retrospectively evaluated brain MR imaging findings of 66 patients who were proved to have LNB on the basis of clinical criteria, serologic results, and response to treatment. Of the 66 patients, 11 showed abnormal findings on MR imaging. Three patients showed nerve-root or meningeal enhancement, 7 patients demonstrated foci of T2-signal abnormality in the cerebral white matter without enhancement, and 1 patient had an enhancing lesion with edema. Of the 7 patients with white matter lesions, the blinded readings indicated that 3 of them had nonspecific lesions that, given the ages of the patients (ranging from 26 to 57 years), were probably small-vessel white matter disease. The remaining 4 patients had abnormalities that were considered unusual for their ages. The investigators concluded that

although Lyme disease has been generally reported to manifest as foci of T2 prolongation in the cerebral white matter, nerve root or meningeal enhancement is also frequently seen and may be equally common. In the literature, third, fifth, and seventh cranial nerve enhancements have all been documented as well as primary leptomeningeal enhancement (see **Fig. 8**).[27,38–42,68] Predominantly, seventh cranial nerve involvement is observed with a "tuft" of enhancement at the fundus of the internal auditory canal and enhancement of the labyrinthine and tympanic segments more than generalized fundal tuft-to-mastoid involvement (**Fig. 9**).[27] This enhancement correlates well with the fact that Lyme disease may be responsible for 25% of new-onset Bell palsy in endemic areas despite it being an infrequent cause of isolated facial palsy in patients without constitutional symptoms or additional neurologic findings.[27,69] Cranial neuropathies as well as motor or sensory radiculoneuritis have their highest incidence in children and adolescents with approximately 3% to 5% occurrence of facial nerve palsy during the course of pediatric Lyme neuroborreliosis.[27] Brain MR imaging findings in pediatric LNB include the presence of prominent Virchow-Robin spaces, T2 bright white matter lesions, pial and cranial nerve enhancement, and treatment-responsive lesion enhancement.

Another rare manifestation of LNB is vasculitis, which may be associated with ischemic stroke,
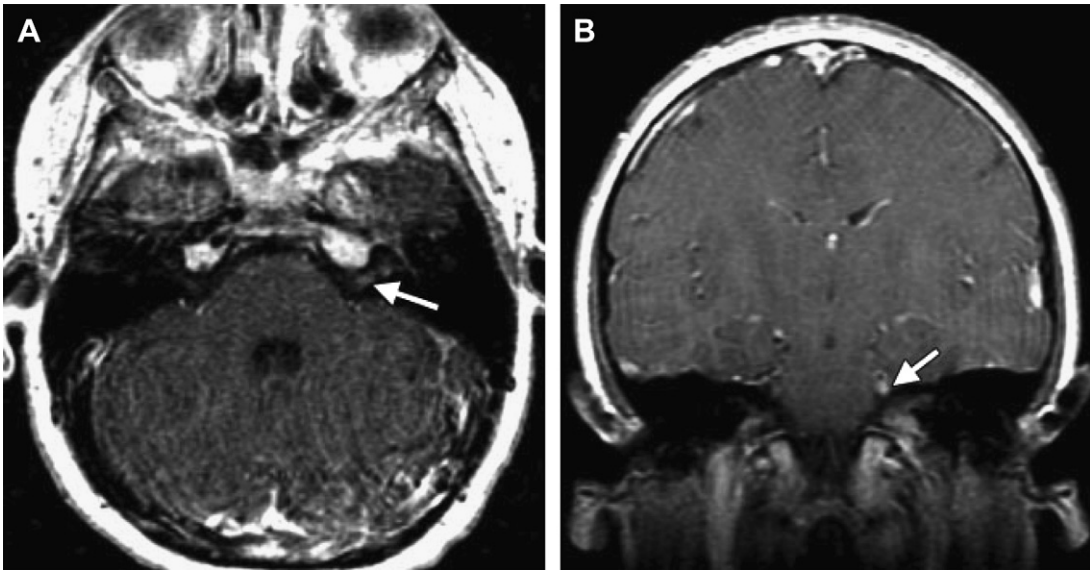
Fig. 9. Lyme disease. Manifestation of palsy of left seventh cranial nerve in a 10-year-old male patient with recent history of camping. (*A*) Transverse T1-weighted post-contrast MR image shows enhancement of left seventh cranial nerve (*arrow*). (*B*) Coronal T1-weighted post-contrast MR image demonstrates left trigeminal nerve enhancement (*arrow*). (*From* Agarwal R, Sze G. Neuro-lyme disease: MR imaging findings. Radiology 2009;253(1):167–73; with permission.)

subarachnoid hemorrhage, and intracerebral hemorrhage.[31,43–48,70]

Although most patients with LNB recover fully when treated with antibiotics, some patients who are treated months after the initial infection may still experience ongoing problems with fatigue, cognition, and pain despite receipt of a standard antibiotic treatment. These patients have been described as having chronic Lyme disease or post-treatment Lyme disease syndrome, which remains an ongoing focus of controversy.[27,71] Continuing symptoms have been attributed to persistent infection, pathogen-induced autoimmunity, or unrelated processes, such as depression, somatization, fibromyalgia, or chronic fatigue syndrome. Aalto and colleagues[72] conducted a study aiming to evaluate brain MR imaging findings of chronic neuroborreliosis with inclusion of age-matched healthy controls for comparison. White matter and basal ganglia lesions were observed in 12 of 16 patients; the findings, although, were nonspecific when compared with matched controls and did not correlate with disease duration. However, the investigators have also concluded that subependymal lesions may constitute a potential finding in chronic neuroborreliosis. Morgen and colleagues[73] analyzed the distribution of cerebral lesions in a cohort of 27 patients with post-treatment Lyme disease syndrome with further evaluation in a subgroup of 8 patients using whole-brain magnetization transfer imaging. They have found that in a portion of patients with post-treatment Lyme disease syndrome, white-matter lesions tend to occur in subcortical arteriolar watershed areas, although still nonspecific. Magnetization transfer ratio analysis did not provide evidence for structural abnormalities of the brain parenchyma in patients with nonfocal disease. Despite the lack of definitive imaging findings that may help identification of patients with chronic neuroborreliosis, a PET study conducted by Fallon and colleagues[71] has demonstrated objectively quantifiable topographic abnormalities in functional brain activity in patients with persistent Lyme encephalopathy with regional cerebral blood flow and regional cerebral metabolic rate reductions observed in all measurement conditions.

Rarely, ocular involvement is also seen during the course of Lyme disease at any clinical stage with conjunctivitis and episcleritis commonly seen during the early stage; optic neuritis and uveitis observed during the second stage; and keratitis, chronic intraocular inflammation, and orbital myositis seen in the third stage of Lyme disease (**Fig. 10**).[27] Although direct infection or a delayed immunologic response may be considered as the underlying mechanism, a hematogenous dissemination followed by an immunologically mediated reaction seems to be the most likely explanation for the muscle inflammation in orbital myositis.[74]
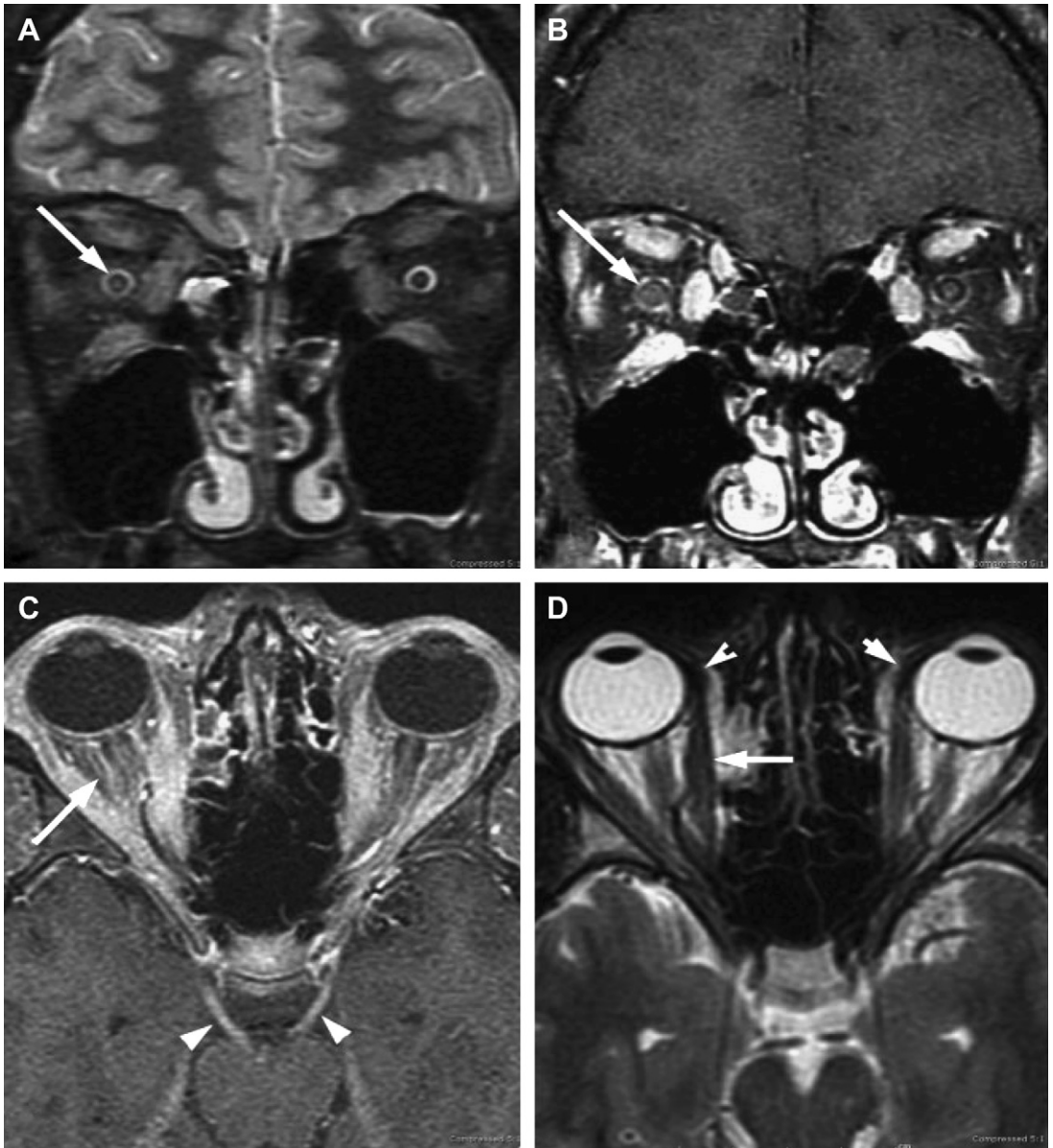
Fig. 10. Lyme disease. A 17-year-old boy with right papilledema and orbital pain and rule out pseudotumor. The patient had positive serum EIA and Western blot (IgM and IgG) and CSF Lyme IgM and IgG antibodies. Lyme PCR in the CSF was negative. Complete resolution of symptoms occurred after intravenous ceftriaxone therapy. Right optic nerve edema (*arrow*) on fat-saturated T2-weighted fast spin-echo images (*A*) and right-greater-than-left optic nerve enhancement (*arrow*) on coronal fat-saturated contrast-enhanced T1-weighted images (*B*). Bilateral third cranial nerve enhancement (*arrowheads*) and bilateral retrobulbar compartment congestion (*arrow*) (*C*). Note the generalized extraocular muscle enlargement and enhancement (*arrow*), including the insertions (*arrowheads*) (*D*). Additional imaging findings included enhancement of right fifth cranial nerve, optic chiasm, and intracanalicular right seventh nerve, all of which were occult to neurologic examination. (*From* Hildenbrand P, et al. Lyme neuroborreliosis: manifestations of a rapidly emerging zoonosis. AJNR Am J Neuroradiol 2009;30(6):1079–87; with permission.)

Lyme disease may closely mimic orbital pseudotumor. In the appropriate clinical presentation and lacking evidence of other disease conditions, Lyme disease should be considered in the differential diagnosis of ocular lesions, as initiation of antibiotic treatment is almost always followed by resolution of the clinical symptoms and radiologic findings.[74,75]

Although lymphocytic meningoradiculitis is the most common clinical manifestation of infection of the CNS in Europe, MR imaging findings of spinal cord involvement have only rarely been demonstrated. Demaerel and colleagues[30] has described diffuse intense enhancement along the thickened nerve roots of the cauda equina in a 10-year-old patient with lymphocytic meningoradiculitis (Bannwarth syndrome) (**Fig. 11**). Later, Pfefferkorn and colleagues[76] demonstrated similar findings in a 50-year-old patient with a post-treatment MR imaging study showing complete resolution of the findings. In addition, Hattingen and colleagues[77] reported cervical MR imaging findings of 2 children with bilateral intense enhancement along cervical nerve roots as a manifestation of Borrelia-associated radiculitis (**Fig. 12**). Mantienne and colleagues[49] described intense leptomeningeal enhancement along the surface of the distal thoracic spinal cord and conus medullaris without accompanying typical radiculitis in a patient with Lyme disease, with

improvement of these findings on follow-up study. Also, a few case reports of transverse myelitis associated with Lyme disease are present in the literature predominantly involving the cervical spinal cord with diffuse signal abnormality associated with enhancement.[50–52] Tullman and colleagues[78] described a case with cervical myelitis accompanied by bilateral cervical radiculitis. Hattingen and colleagues[77] noted lack of a close correlation between neurologic symptoms and imaging findings.[77]

Relapsing Fever

Relapsing fever in epidemic form is caused by Borrelia recurrentis, which is transmitted to humans by the human body louse and does not occur in the United States.[2] Endemic relapsing fever is caused by Borrelia transmitted by ticks of the genus Ornithodoros. After a short incubation period of 3 to 10 days, disease presents with sudden chills and an abrupt fever. The fever may persist for 3 to
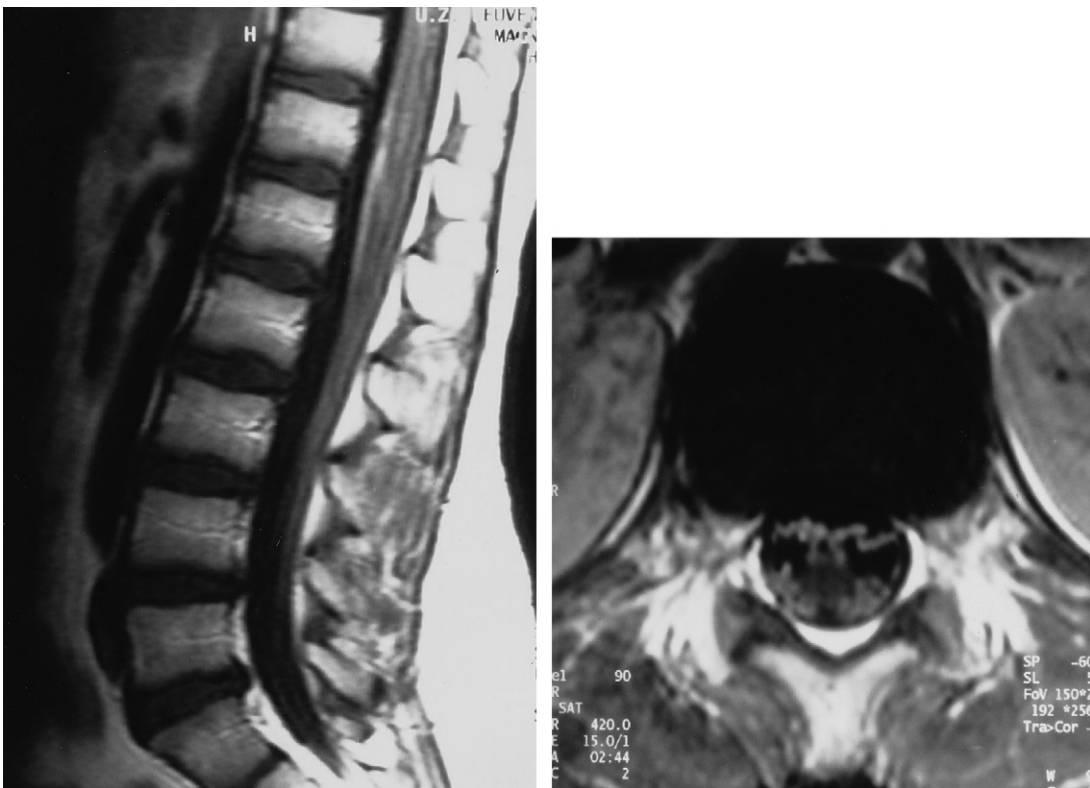

Fig. 11. Lyme disease. A 10-year-old boy presented with a 3-week history of right-sided low back pain radiating to the leg. There were no neurologic signs or fever at first presentation. There was progressive improvement of the symptoms. However, 2 months after his first presentation, the child was admitted with neurologic signs: weakness in the right leg with absent patellar and Achilles reflexes. Heel walking was limited whereas toe walking was normal. Lumbar spine MR imaging revealed enhancement of thickened nerve roots of the cauda equina on contrast-enhanced T1-weighted sagittal and axial images. (*From* Demaerel P, et al. Meningoradiculitis due to borreliosis presenting as low back pain only. Neuroradiology 1998;40(2):126–7; with permission.)
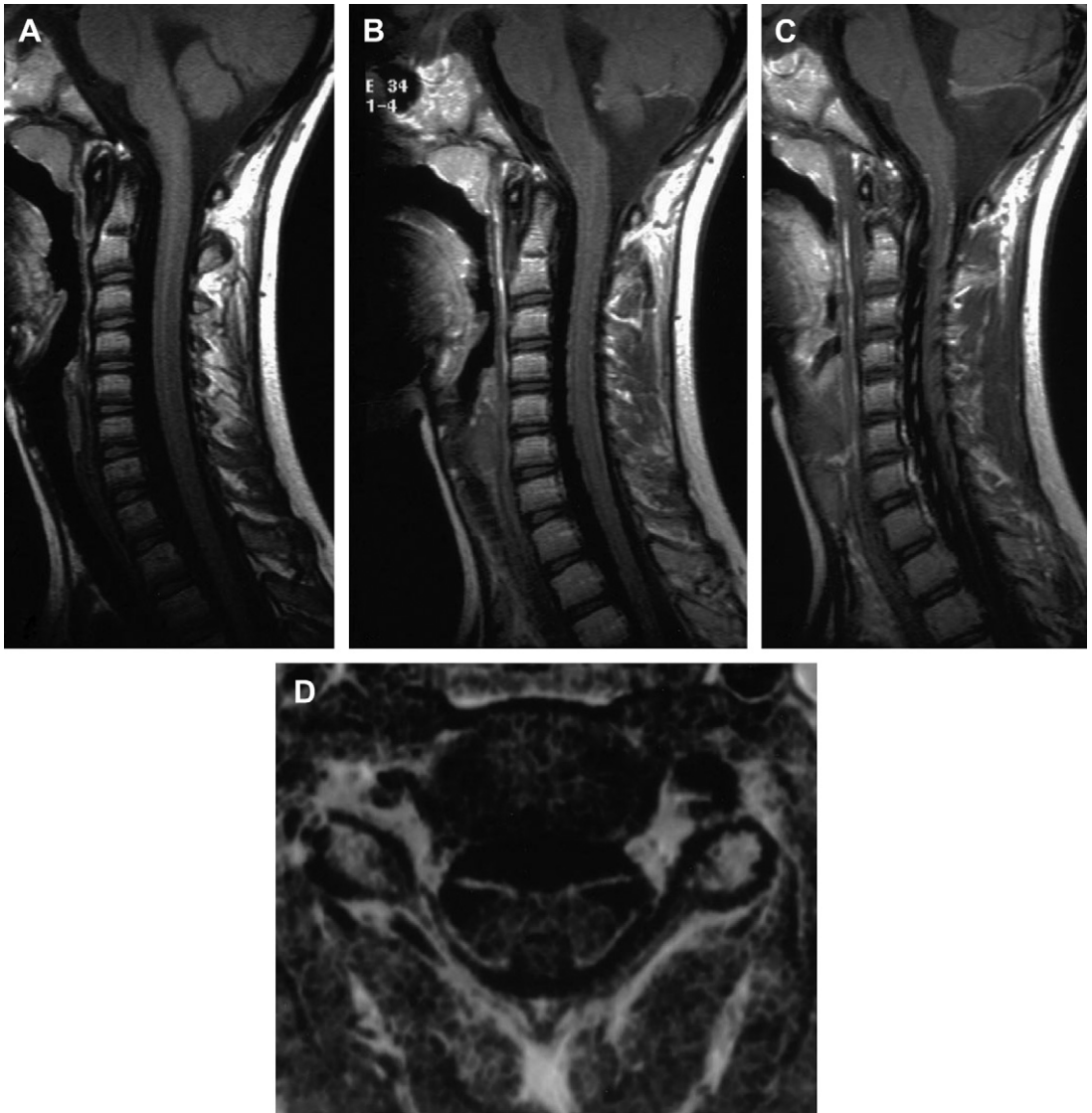
Fig. 12. Lyme disease. (*A–D*) Sagittal T1-weighted images (TR/TE = 870/18) before (*A*) and after (*B*) intravenous administration of 0.1 mmol/kg gadopentetate dimeglumine diethylene triamine pentaacetic acid in the midline of the cervical spinal cord revealing slight pial enhancement. Contrast-enhanced paramedian sagittal (*C*) and axial (*D*) T1-weighted images (TR/TE 513/12) demonstrate strong enhancement of the cervical and upper thoracic nerve roots. *Abbreviations:* TE, echo time; TR, repetition time. (*From* Hattingen E, et al. MR imaging in neuroborreliosis of the cervical spinal cord. Eur Radiol 2004;14(11):2072–5; with permission.)

5 days and then declines, followed by an afebrile period lasting approximately 4 to 10 days. Then, the cycle begins by a second attack of chills, fever, intense headache, and malaise repeating approximately 3 to ten times, generally of diminishing severity. During the febrile stages, organisms are present in the blood; however, while during the afebrile periods, they are absent. Fatal cases show spirochetes in great numbers in the spleen and liver, necrotic foci in other parenchymatous organs, and hemorrhagic lesions in the kidneys and the gastrointestinal tract. Spirochetes have occasionally been demonstrated in the spinal fluid and brain of persons who have had meningitis.[2] There is no known corresponding neuroimaging finding documented in the literature.

Leptospirosis

The pathogenic species is Leptospira interrogans with a worldwide distribution. The leptospiroses are essentially animal infections; human infection

is only accidental, following contact with water or other materials contaminated with the excreta of animal hosts, including rats, mice, wild rodents, dogs, swine, and cattle.[2] Leptospirae remain viable in stagnant water for several weeks; drinking, swimming, bathing, or food contamination may lead to human infection. Humans usually acquire infection from ingestion of water or food contaminated with leptospirae. More rarely, the organisms may enter through mucous membranes or breaks in the skin.[10] After an incubation period of 1 to 2 weeks, there is a variable febrile onset during which spirochetes are present in the bloodstream. Then, parenchymatous organs, particularly liver and kidneys, are involved with hemorrhage and tissue necrosis resulting in dysfunction of those organs (jaundice, hemorrhage, nitrogen retention). After initial improvement, the second phase develops when the immunoglobulin M (IgM) antibody titer rises. It manifests itself often as "aseptic meningitis" with intense headache, stiff neck, and pleocytosis of the cerebrospinal fluid. Nephritis and hepatitis may also recur, and there may be skin, muscle, and eye lesions. The degree and distribution of organ involvement vary in the different diseases produced by different leptospirae in various parts of the world. Many infections are mild or subclinical.

A few case reports are present in the literature describing rare occurrences of acute disseminated encephalomyelitis following leptospirosis.[79,80] Maldonado and colleagues[81] reported a patient who presented with bilateral Bell palsy on day 15 during the course of leptospirosis that he developed while returning from a 5-month trip to China. Given the delay of onset of facial palsy, investigators have suggested vasculitis rather than a direct neurotoxic effect as underlying mechanism. In addition, Habek and Brinar[82] documented an inhomogeneously enhancing pontomedullary brainstem lesion in a patient with central sleep apnea and ataxia who received diagnosis of neuroleptospirosis after 2 years from the initial disease presentation, and the brainstem lesion remained stable throughout those years under corticosteroid treatment.

EUKARYOTIC PARASITES
Amebiasis

Amoeba is a genus of protozoa (from the Greek words "proton" meaning first and "zoa" meaning animals). Protozoans are single-celled nonfungal eukaryotes, eukaryotes being distinguished from prokaryotes (Archaea and bacteria) by the presence of a nucleus.

CNS amebiasis is a rare condition that can be caused by several free living amoebic organisms including Naegleria fowleri and Acanthamoeba species.[14] Naegleria and Acanthamoeba organisms are responsible for causing primary amoebic meningoencephalitis and granulomatous amoebic meningoencephalitis (**Fig. 13**), respectively, with a distinctive epidemiology, pattern of presentation, clinical course, pathology, and imaging findings.[83] In contradistinction is Entamoeba histolytica, a relatively common intestinal parasite endemic to the Southern United States, South
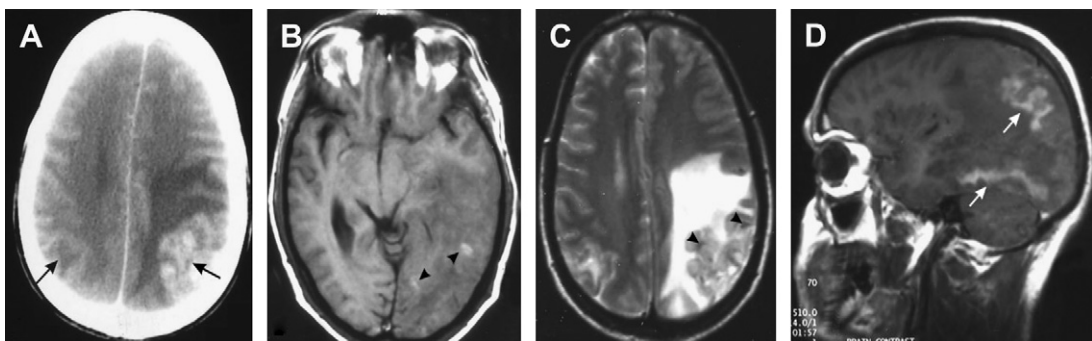

Fig. 13. Granulomatous amoebic meningoencephalitis. A 38-year-old man with deteriorating vision and persistent vomiting for a week (granulomatous amoebic encephalitis). (*A*) Contrast-enhanced CT scan of the brain shows an enhancing cortical-based lesion in the left parietal lobe with extensive perilesional edema. Another smaller hypoattenuated lesion is seen on the opposite side (*arrows*). (*B*) T1-weighted MR image shows hemorrhagic foci (*arrowheads*) in the left parietooccipital lesion with ill-defined gray-white matter distinction. (*C*) T2-weighted MR image shows heterogeneous signal intensity in the swollen cortex (*arrowheads*) with extensive white matter edema. The right-sided lesion also shows mild edema and cortical signal intensity changes. (*D*) Contrast-enhanced T1-weighted sagittal image shows gyriform enhancement of the affected cortex with nonenhancing edematous white matter. Similar enhancement is also seen in the undersurface of the occipital lobe (*arrows*). (*From* Singh P, et al. Amoebic meningoencephalitis: spectrum of imaging findings. AJNR Am J Neuroradiol 2006;27(6):1217–21; with permission.)

America, Latin America, Southeast Asia, and Africa, which is transmitted to humans via fecal-oral contamination and can rarely present with CNS involvement.[14,84] The organism is thought to reach the CNS via the blood stream through the hepatic, pulmonary, or vertebral veins.[10] Isolated CNS involvement is rare. Many patients with CNS disease may also have liver abscesses and/or concomitant gastrointestinal and pulmonary symptoms that may provide a clue for the diagnosis. Secondary cerebral amebiasis lesions could be single or multiple with central necrosis and often accompanied by hemorrhage.[14] Cortical and deep gray matter is frequently involved, particularly the frontal lobes and basal ganglia. Focal or generalized meningitis can also be observed.[14] Imaging findings described in a few case reports correlate well with pathologic findings with single or multiple ring-enhancing lesions demonstrated on CT and/or MR images. Although prognosis is poor, early treatment with metronidazole and if necessary prompt surgical intervention may improve the outcome.[14,84]

Naegleria fowleri is the causative agent for primary amoebic meningoencephalitis, which is a rapid onset fulminant infection of the brain, and meninges presenting with severe headache, fever, nausea, vomiting, ataxia, diplopia, photophobia, stiff neck with rapid progression to stupor and coma, and eventually death in several days in most cases.[83,85,86] Affected population is children and young adults without immunologic compromise.[83] The organism is found anywhere; however, the most frequent method of disease exposure for humans is by swimming in stagnant pools of warm freshwater, typically in summer months.[86] The organism gains access into the CNS via penetration of the olfactory neuroepithelium and then disseminates through the subarachnoid space and into the adjacent cerebral cortex at the base of the brain.[86] Corresponding pathologic changes include extensive damage to the brain parenchyma, ependyma, and meninges with congestion of the meningeal vessels, edematous cortex with herniation of uncus and cerebellum.[83] Microscopically, there is a purulent leptomeningeal exudate with hemorrhage and necrosis throughout the cerebral hemispheres, brain stem, cerebellum, and upper spinal cord. Imaging findings are rarely described and essentially nonspecific. CT and MR imaging findings may be normal during early disease with later development of brain edema (**Fig. 14**), hydrocephalus, and basilar meningeal enhancement.[83,86] Singh and colleagues[83] additionally documented basal ganglia infarction, which they linked to possible obliteration of the perforating vessels by the extensive exudates (**Fig. 15**).

The Acanthamoeba and Leptomyxa genera including Balamuthia mandrillaris can cause granulomatous amoebic encephalitis, which is a subacute to chronic infection and predominantly known to occur in patients who are debilitated or immunocompromised by AIDS, chemotherapy, or steroid therapy.[83,85] Unlike Naegleria fowleri, these amoebae secondarily infect the CNS, possibly from the lower respiratory tract, genitourinary tract, or skin.[86] Symptoms frequently resemble those of single or multiple space-occupying CNS lesions. Pathologically, infection is characterized by multifocal areas of hemorrhagic necrosis, edema, and abscess formation with predilection to the posterior fossa structures, the thalamus, and the brainstem with frequent involvement of the cerebral hemispheres. Microscopically, as the name implies, lesions demonstrate chronic granulomatous-type reaction with focal necrosis and hemorrhage. There may be severe necrotizing angiitis.[86] According to the published case reports to date, CT and MR imaging findings in granulomatous amoebic encephalomyelitis are either in the form of a multifocal pattern with discrete focal lesions in the corticomedullary junction, deep gray matter, or brainstem or as a larger solitary masslike lesion or a combination of the 2 findings.[83,85,87–91] Singh and colleagues[83] reported that a masslike lesion, which they called a pseudotumoral pattern, often demonstrates a linear and superficial gyriform pattern of enhancement, which could be a useful indicator of the diagnosis.

Schistosomiasis

Schistosomiasis, also known as bilharziasis, is a chronic human trematode infection affecting at least 200 million people worldwide. This infection is endemic to Africa, South America, Middle East, and most parts of Asia.[92] The disease typically involves urogenital, intestinal, and hepatolienal organs and may lead to severe liver disease with fibrosis and portal hypertension as well as bladder, liver, and rectal carcinoma.[93] Schistosoma haematobium, Schistosoma mansoni, and Schistosoma japonicum are the 3 main subspecies affecting humans. Schistosoma species have a complex life cycle beginning with the release of cercariae into streams or lakes by freshwater snails (the intermediate hosts), which then penetrate the human skin and migrate to the lungs and liver, where they mature to form mating pairs of male and female adult worms in the mesenteric veins.[94] Ectopic migration of the worms and oviposition can occur, resulting in a variety of lesions outside the gastrointestinal
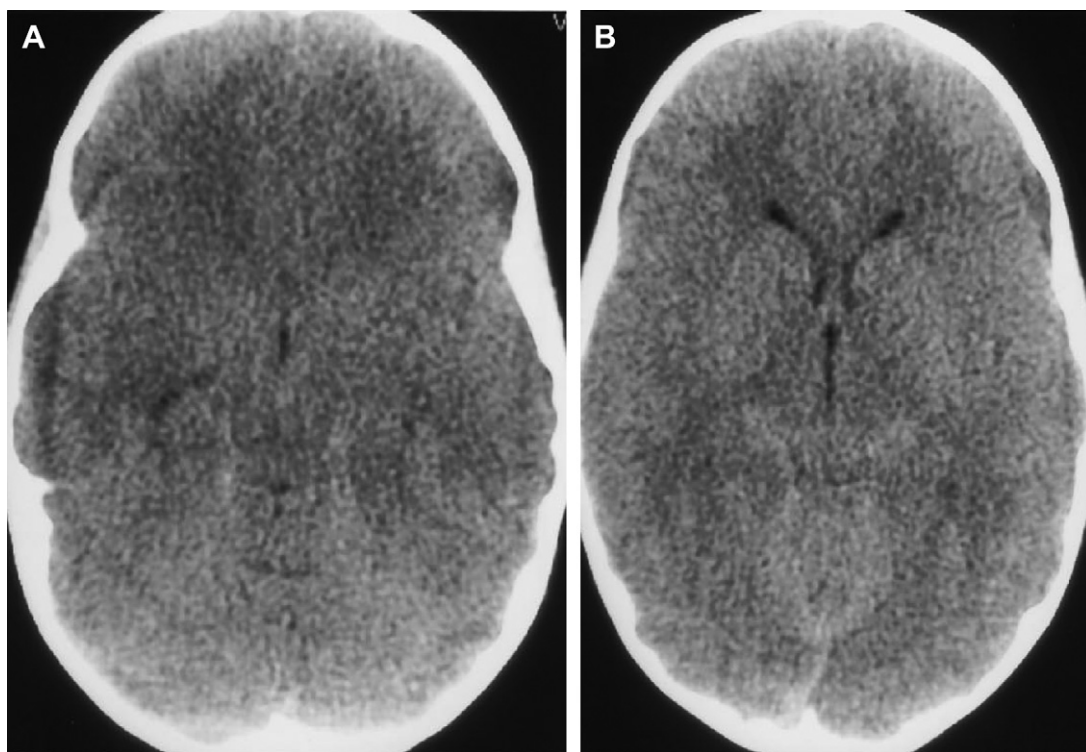
Fig. 14. Amebiasis_ Naegleria fowleri. (*A*) Noncontrast CT at the level of the temporal horns showing effacement of perimesencephalic cisterns. (*B*) Noncontrast CT at the level of the superior colliculus showing effacement of the quadrigeminal plate cistern. Sulci could not be identified anywhere in the cerebral cortex. At autopsy, Naegleria fowleri were identified in the subarachnoid space in this patient with panamebic meningoencephalitis. (*From* Schumacher DJ, Tien RD, Lane K. Neuroimaging findings in rare amoebic infections of the central nervous system. AJNR Am J Neuroradiol 1995;16(Suppl 4):930–5; with permission.)

system, including the lungs and CNS, with Schistosoma japonicum typically affecting the brain, whereas Schistosoma mansoni and Schistosoma hematobium infections characteristically result in spinal cord lesions.[93] The clinical manifestations of cerebral schistosomiasis are variable, including acute encephalopathy, seizures, paresis, headache, and visual disturbances.[10] Liu and colleagues[93] have investigated brain MR imaging findings in 33 patients with a presumptive diagnosis of cerebral schistosomiasis caused by Schistosoma japonicum, and discovered a common pattern of large discrete lesions with prominent perilesional edema with the lesions composed of multiple small enhancing nodules, sometimes with areas of linear enhancement (**Fig. 16**). Although not present in all cases, when this arborized pattern, which is also described by Wan and colleagues[94,95] as the Buddha's hand appearance, is observed, a diagnosis of cerebral schistosomiasis should be considered. This nodular pattern of contrast enhancement was also commonly documented in spinal schistosomiasis along with peripheral

enhancement and linear radicular enhancement in some patients and was correlated to multiple schistosomiasis microtubercles.[92] Saleem and colleagues[92] have concluded that schistosomiasis of the spinal cord should be considered in the differential diagnosis of lesions involving the lower thoracic cord, conus medullaris, and cauda equina in patients from endemic areas with history of exposure to schistosomal infestation particularly in the presence of intramedullary nodular enhancement described earlier (**Fig. 17**).

Toxoplasmosis

CNS toxoplasmosis is caused by Toxoplasma gondii, an intracellular protozoan that is found worldwide. It is transmitted to humans primarily by ingestion of cysts in undercooked pork or lamb or vegetables contaminated with cat feces or via transplacental infection.[14,96] Immunocompetent individuals with an acute infection are usually asymptomatic or may have a mononucleosis syndrome early in the disease. Following acute infection, a latent phase ensues that is
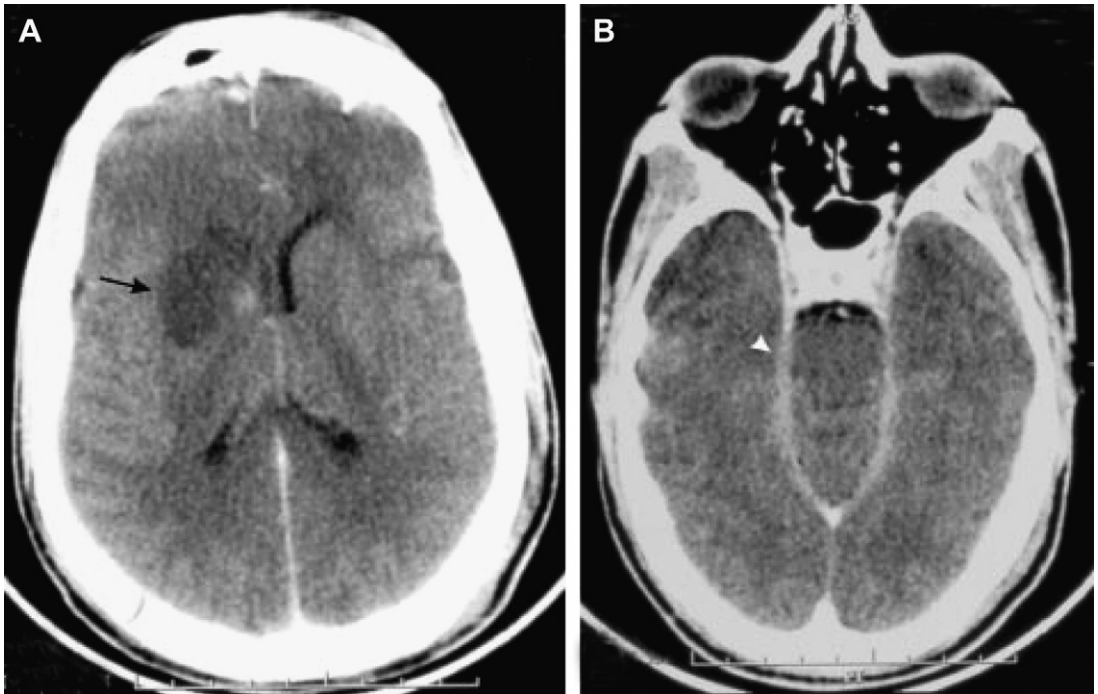
Fig. 15. Amebiasis_ Naegleria fowleri. A 40-year-old man who presented with fever and headache for a week and altered sensorium for 3 days (primary amoebic meningoencephalitis). Contrast-enhanced CT brain scan shows right basal ganglia infarction (*arrow, A*) and enhancing exudates in the perimesencephalic cistern (*arrowhead, B*). (*From* Singh P, et al. Amoebic meningoencephalitis: spectrum of imaging findings. AJNR Am J Neuroradiol 2006;27(6):1217–21; with permission.)

characterized by silent persistence of the organisms primarily in the brain, skeletal muscle, and heart.[96] Toxoplasma gondii seropositivity for adults in the United States varies between 20% and 70%.[14] These dormant organisms normally are not expected to reactivate unless these individuals develop defects in cell-mediated immunity such as in the presence of AIDS. Therefore, in clinical practice, toxoplasmic encephalitis cases are almost always secondary to reactivation of a latent
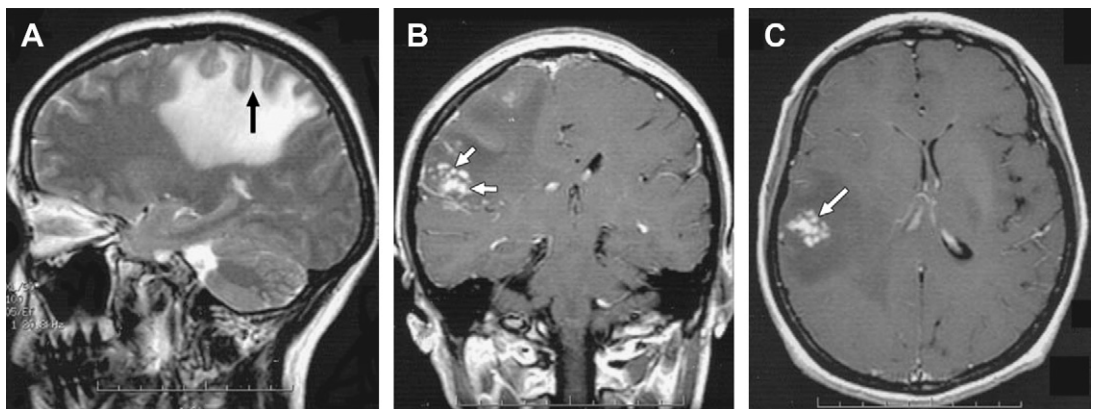

Fig. 16. Cerebral schistosomiasis. A 47-year-old woman with cerebral schistosomiasis and 2-week history of headache and seizures. Sagittal T2-weighted MR image shows prominent vasogenic edema in frontal and parietal lobes, with well-defined deep surface and fingerlike projections (*arrow, A*) into subcortical white matter. Axial and coronal T1-weighted images (*B, C*) after intravenous administration of contrast material show multiple intensely enhancing small nodules, 1 to 3 mm in diameter (*arrows*), clustered closely together. Second cluster in right frontal lobe superiorly is poorly seen because of partial volume effects. (*From* Liu H, et al. MRI in cerebral schistosomiasis: characteristic nodular enhancement in 33 patients. AJR Am J Roentgenol 2008;191(2):582–8; with permission.)
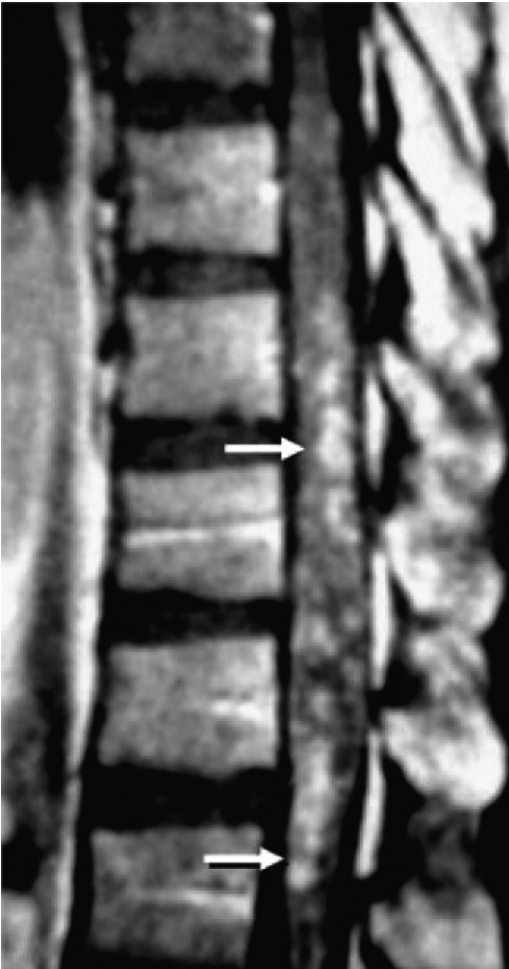
Fig. 17. Spinal schistosomiasis. Diffuse nodular enhancement form in spinal cord schistosomiasis. Post-contrast sagittal T1-weighted spin-echo MR image (TR/TE 520/20 ms) showing multiple small intramedullary enhancing nodules diffusely involving the distal thoracic cord and conus medullaris (*arrows*). (*From* Saleem S, Belal AI, el-Ghandour NM. Spinal cord schistosomiasis: MR imaging appearance with surgical and pathologic correlation. AJNR Am J Neuroradiol 2005;26(7):1646–54; with permission.)

disease. In fact, toxoplasmic encephalitis is the most common cause of brain space-occupying lesions in AIDS patients and may follow a progressive fatal course, if left untreated.[14] However, with the institution of prophylactic treatment against toxoplasmosis along with induction of highly active antiretroviral therapy, there has been decline in the occurrence of opportunistic infections.[97]

Pathologically, 3 types of focal lesions are described in toxoplasmic encephalitis including necrotizing abscesses, organizing abscesses, and chronic abscesses. In addition, 3 distinct

zones are recognized in parencyhmal toxoplasma lesions: (1) a central avascular zone reflecting coagulative necrosis; (2) an intermediate zone engorged with blood vessels and containing numerous tachyzoites, which corresponds to the enhancing ring seen on CT and/or MR images; (3) and a peripheral zone with few vascular changes and more encysted bradyzoites, which may appear as edema on neuroimaging studies.[14] Solitary lesions may occur in one-third of the cases; however, most commonly the lesions are multiple with predilection for the basal ganglia (in 75%–88% of cases), thalamus, and gray-white junction of cerebral hemispheres, particularly in the frontal and parietal lobes.[14] An "eccentric target sign" is described that is essentially a small eccentric nodule along the ring-shaped zone of peripheral enhancement and considered to be suggestive of cerebral toxoplasmosis, although not seen commonly in neuroimaging studies (**Fig. 18**). Ramsey and colleagues[98] suggested that it might be related to focal invagination or folding of the cyst wall on itself. According to them, toxoplasmosis lesions may lack obvious contrast enhancement in the brain of the
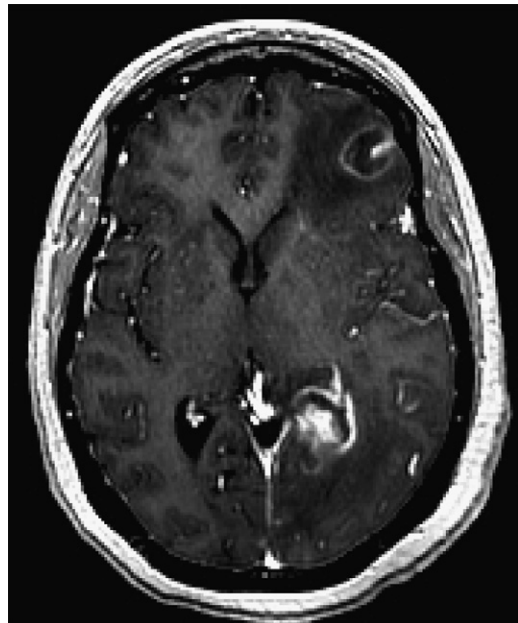

Fig. 18. Toxoplasmosis eccentric target sign. A 47-year-old woman presented with low grade fever and confusion. MR imaging demonstrated multiple rim enhancing lesions, which were found to be CNS toxoplasmosis in the setting of a newly diagnosed human immunodeficiency virus with a CD4 count of 14 and a viral load of 229,660. Contrast-enhanced T1-weighted 3D spoiled gradient recalled echo image shows left frontal and left medial occipital rim enhancing lesions with characteristic eccentric target signs.

immunocompromised patients, despite severe disease involvement (**Fig. 19**).[99,100]

Despite advances in imaging techniques, a correct diagnosis of mass lesion in an AIDS patient is still a dilemma, particularly with differentiation from primary brain lymphoma lesions.[14] Nuclear studies such as thallium-201 brain single-photon emission computed tomography and ^{18}F-FDG PET may aid in differentiation as toxoplasmosis lesions are not hypermetabolic.[101,102] Diffusion-weighted imaging may also be helpful in differentiating these 2 conditions, given the known hypercellular nature of lymphoma lesions that may result in reduction of apparent diffusion coefficient (ADC) values.[14,103] Furthermore, Chong-Han and colleagues[104] have evaluated ADC values in cerebral toxoplasmosis lesions and found that unlike pyogenic abscesses, the central core of rim-enhancing toxoplasma abscesses demonstrate facilitated water diffusion, which correlates well with the fact that the core of a toxoplasma abscess consists primarily of necrotic tissue and does not have the viscous, proteinaceous, and inflammatory debris of purulent fluid. However, in contrast, Schroeder and colleagues[105] have concluded that in most patients, ADC ratios are not definitive in making the distinction because toxoplasmosis exhibits a wide spectrum of diffusion characteristics that have significant overlap with those of lymphoma. Dynamic perfusion MR imaging has also been proposed as a means of distinguishing these conditions with a relatively decreased relative cerebral blood volume in toxoplasma lesions in comparison to lymphoma lesions, which could be related to a relative lack of vasculature within the abscess.[106] MR spectroscopy may also be helpful in differentiation with the spectra in toxoplasmosis commonly revealing elevated lipid and lactate peaks in the absence or dramatic reduction of other normal brain metabolites, in contrast to a commonly seen spectra of lymphoma demonstrating mild-to-moderate increase in lipid and lactate peaks, a markedly elevated choline peak with relative preservation of the normal metabolites.[14]

Hydatid Disease

Hydatid disease is a parasitic infection caused by a tapeworm Echinococcus. There are 2 types of echinococcus infections: Echinococcus granulosus is the more common type, whereas Echinococcus multilocularis is less common but more invasive, usually mimicking a malignancy.[107] Hydatid disease remains endemic to some parts of the world, most notably the Mediterranean region, Middle East, South America, New Zealand, and Australia. Dogs or other carnivores are definitive hosts, whereas sheep or other ruminants are
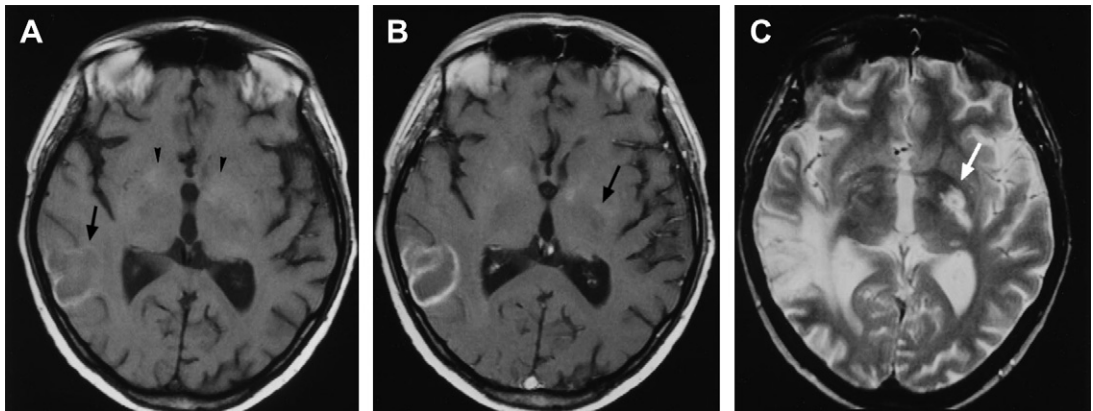

Fig. 19. Toxoplasmosis in immunosuppressed bone marrow transplant patient. A 31-year-old man had allogeneic bone marrow transplant (BMT) for treatment of chronic myeloid leukemia. On day 65, after BMT, he had focal seizures with secondary generalization, dysarthria, and mild cerebellar ataxia. MR imaging revealed: (*A*) Axial T1-weighted image reveals a low-signal temporal lesion with an incomplete high-signal ring suggesting a necrotic infectious lesion (*large arrow*). Bilateral foci of high signal in the basal ganglia (*arrowheads*) were thought to be due to calcium or manganese. (*B*) There is moderate ring enhancement of the right temporal lesion and only faint enhancement of a left basal ganglion lesion (*small arrow*). (*C*) Perifocal edema is better seen on T2 weighting (*white arrow*). This helped to distinguish between metabolic and infectious basal ganglion changes. Serologic tests were positive for IgG antibodies against Toxoplasma gondii but negative for IgM antibodies. Antitoxoplasmosis treatment was started with pyrimethamine and sulfadiazine. MR imaging 10 days later revealed only partial regression of the right temporal lesion, and stereotactic biopsy was performed to rule out other infectious agents. Histology confirmed necrotising encephalitis, suggestive of toxoplasmosis. (*From* Dietrich U, et al. MRI of intracranial toxoplasmosis after bone marrow transplantation. Neuroradiology 2000;42(1):14–8; with permission.)
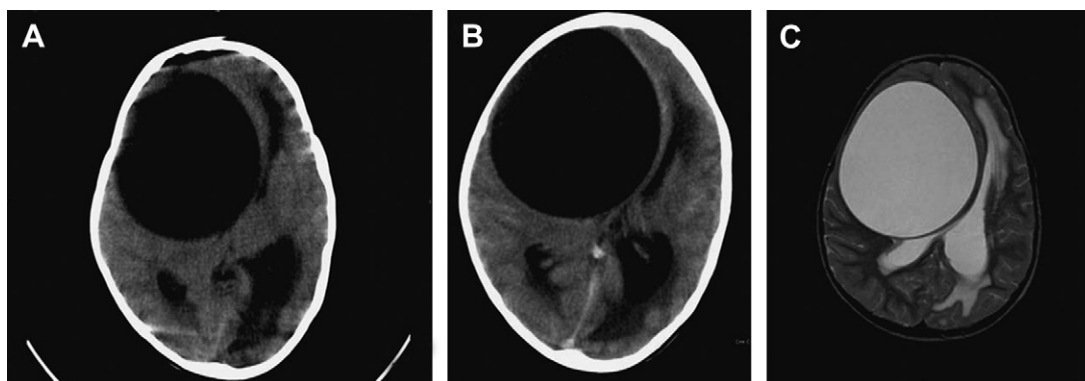
Fig. 20. Hydatid disease. (*A*) Plain CT, (*B*) contrast CT, and (*C*) T2-weighted MR image large cystic lesion with no evidence of enhancement or edema. The periventricular hyperintensity on the left is because of obstructive hydrocephalus. (*From* Kovoor JM, Thomas RD, Chandrashekhar HS, et al. Neurohydatidosis. Australas Radiol 2007;51(5):406–11. Copyright © 2007. This material is reproduced with permission of John Wiley & Sons, Inc.)

intermediate hosts. Humans are secondarily infected by the ingestion of food or water that has been contaminated by dog feces containing the eggs of the parasite.[107] The overall incidence of organ infestation is greatest in the liver (50%–77%) and lungs (8.5%–43%). Involvement of the CNS is rare and occurs in about 3% of all hydatid disease.[108] Cerebral hydatid disease is most commonly diagnosed in children (approximately 50%–70% of cases).[109] Histopathologically the wall of the Echinococcus granulosus cyst consists of an inner germinal layer (endocyst) and an outer laminated layer (ectocyst). The host reacts to the cyst by forming a fibrous capsule (pericyst), with vascularization thus providing nutrients for the parasite. In the brain, the pericyst is thin because of minimal host reaction.[110] Most Echinococcus granulosus cysts are usually solitary and most commonly supratentorial, within the middle cerebral artery territory.[14] Lesions usually appear as well-defined, smooth, thin-walled, spherical, homogeneous cystic lesions with the appearance of the cyst fluid similar to that of cerebrospinal fluid.[111] On unenhanced CT, the cyst wall is isodense or hyperdense to brain tissue. The cyst wall usually shows a rim of low signal intensity on both T1- and T2-weighted images; in particular, on T2-weighted MR imaging, the presence of a hypointense rim has been described as characteristic of cerebral hydatidosis.[14] Usually no enhancement or surrounding edema is evident unless the hydatid cyst is superinfected (**Fig. 20**). Calcification of the wall is rare, being less than 1%. The observation of daughter cysts is considered pathognomonic but has been very rarely reported.[111] Multiple cerebral hydatid cysts are relatively rare and result from spontaneous, traumatic, or iatrogenic rupture of a solitary cerebral cyst or as a consequence of a cyst rupture elsewhere and hematogenous dissemination of organisms to the brain.[108,112] In contrast to Echinococcus granulosus cysts, the cyst of Echinococcus multilocularis grows by external budding of germinal membrane with progressive infiltration of the surrounding tissue. Furthermore, a multilocularis hydatid has little fluid with a semi-solid structure and many small vesicles are embedded in a dense connective tissue stroma.[110] Calcification and surrounding edema are common.[111]

Spinal hydatid disease is rarely seen and occurs in fewer than 1% of all cases of hydatid disease (**Fig. 21**). Thoracic disease is most commonly seen with mainly vertebral and paravertebral involvement as a result of portovertebral shunts.[108]

Fig. 21. Spinal hydatid disease. A 47-year-old man with left lower extremity pain attributed to lumbar hydatid disease. Enhanced CT scan shows multiple paravertebral hydatid cysts. (*From* Tuzun M, Hekimoglu B. Hydatid disease of the CNS: imaging features. AJR Am J Roentgenol 1998;171(6):1497–500; with permission.)

Usually, cysts are multiple with a cystic fluid resembling that of CSF without abnormal enhancement. Lack of lucency or sclerosis within the adjacent bone and absence of disc disease in vertebral hydatid disease may aid in differentiating from tuberculous spondylitis.[108]

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