Review Article

Stroke in central nervous system infections

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Abstract

Background: Stroke subtypes and etiology may differ between developing and developed countries. Infections are a relatively common cause of stroke in tropical regions. **Objective:** To review the main infectious diseases associated with stroke. **Discussion:** Prevalence of stroke in HIV patients is around 1%. Pathogenic mechanisms include HIV vasculopathy, vasculitis, cardioembolism, acquired hypercoagulability, and the effect of opportunistic infections. Treatment with protease inhibitors has been associated with premature atherosclerotic vascular disease. Emerging viral infections that are associated with stroke include viral hemorrhagic fevers, Japanese encephalitis, dengue, and West Nile virus. Vasculitis involving perforating vessels of the brain is a cerebrovascular complication of tuberculous meningitis. Small, medium, and large arteries of the anterior circulation can be involved. A progressive intracranial arteriopathy after *Leptospira interrogans* infection has been described, which involves the large intracranial arteries. Cerebrovascular complications of mycosis are associated with large vessel vasculitis, direct vessel damage by invasion or embolization, and subarachnoid hemorrhage due to mycotic aneurysm rupture. Pathological findings of cerebral malaria include diffuse cerebral edema, perivascular ring hemorrhages, white matter necrosis, parenchyma petechial hemorrhages, occlusion of brain vessels, and sequestration of infected erythrocytes in cortical and perforating arteries. Stroke can occur in subarachnoid neurocysticercosis and the lesions in such cases consist mostly of deep lacunar infarctions resulting from endarteritis of small penetrating arteries. Cardiac arrhythmias, congestive heart failure, apical aneurysm, and mural thrombus are the conditions that predispose patients with American trypanosomiasis to cardioembolism. *Gnathostoma spinigerum* infestation is a cause of hemorrhagic stroke in Asia. **Conclusion:** Infectious and tropical diseases should be included in the differential diagnoses of stroke.

Keywords

AIDS, infectious diseases, neurocysticercosis, stroke, tuberculosis

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Stroke caused an estimated 5.7 million deaths in 2005, and at least two-thirds of them occurred in developing countries.[1] The morbidity rates and psychosocial impact in stroke are also very high. The causes of stroke and the pattern of stroke subtypes differ between developing and developed countries. Infectious diseases are common in tropical regions of the world; some central nervous system (CNS) infections can provoke stroke.[2] The objective of this paper is to review the main viral, bacterial, and parasitic infectious diseases, including some emerging diseases, associated with stroke, [Table 1].

Human immunodeficiency virus (HIV)

The occurrence of stroke in patients with HIV infection has been associated with opportunistic infections, tumors (CNS lymphoma), and advanced stages of immunosuppression.[3] This trend is undergoing major changes. Effective antiretroviral regimens and the introduction of highly active antiretroviral therapy (HAART) have reduced HIV mortality and morbidity. As HIV-infected patients are living longer, an increase of cerebrovascular complications may be expected[3] [Figure 1].

The frequency of stroke (ischemic and hemorrhagic) in HIV-autopsy series ranges between 6 and 34%. However, many pioneer studies did not distinguish between cerebral infarcts associated with opportunistic infections, CNS lymphoma, or cardioembolic sources, and those strokes occurring in the absence of these conditions.

The prevalence of clinically diagnosed stroke in AIDS patients has been estimated to be 1% (range: 0.5-4%), with ischemic stroke constituting at least 70% of the cases.[4-6]

Many HIV-stroke patients are young and immunocompromised, and the prevalence of the classical risk factors in them is low. Pathogenic mechanisms in HIV-associated ischemic stroke include cardioembolism, acquired hypercoagulability, infections, vasculitis, and HIV vasculopathy [Table 2].

Dilated cardiomyopathy is relatively common in the later stages of HIV infection. Cardioembolism may be responsible for stroke in around 20% of these patients.[5] Thrombophilia studies have shown a high prevalence of

Table 1: Infectious and tropical causes of stroke.

Disease	Distribution	Stroke subtype
1. Viral diseases		
AIDS	Worldwide	Cerebral infarcts, vasculitis, intracranial hemorrhage
Viral hemorrhagic fevers	Asia, Africa, Central/South America	Parenchymal and subarachnoid hemorrhages
West Nile virus	North America, Europe, Africa	Ischemic stroke due to vasculitis
Varicella-zoster virus	Worldwide	Ischemic stroke due to vasculitis
2. Bacterial infections		
Tuberculosis	Worldwide	Ischemic stroke due to vasculitis
Leptospirosis	Asia	Parenchymal and subarachnoid hemorrhages
	Central/South America	Moya moya-like syndrome
Infective endocarditis	Worldwide	Cardioembolic infarcts, fusiform aneurysms Parenchymal and subarachnoid hemorrhages
3. CNS mycosis		
Aspergillosis, cryptococcosis, mucormycosis	Worldwide	Ischemic stroke due to vasculitis, fusiform aneurysm, parenchymal and subarachnoid hemorrhages
4. Parasite infections		
Cerebral malaria	Africa, Asia, Central/South America	Ischemic stroke, parenchymal hemorrhages
Neurocysticercosis	Asia, Africa, Central/South America	Ischemic stroke due to vasculitis. Parenchymal and subarachnoid hemorrhages
Chagas' disease	Central/South America	Ischemic stroke
Gnathostomiasis	Asia, Central America	Parenchymal and subarachnoid hemorrhages
5. Other tropical causes		
Snake bites	Worldwide	Ischemic stroke Parenchymal and subarachnoid hemorrhages
Sickle-cell disease	Africa, Central/South America	Ischemic and hemorrhagic strokes

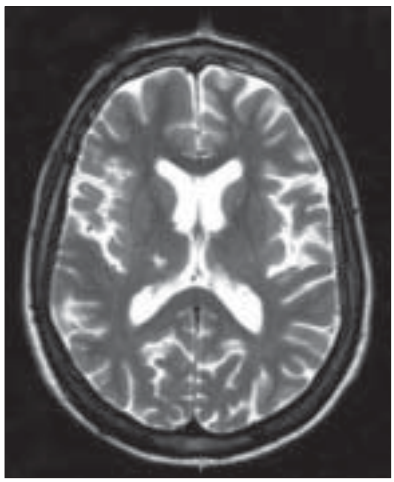

Figure 1: CT scan. Basal ganglia lacunar infarction in a HIV-positive patient

coagulopathy disorders, including the presence of protein S deficiency and positive anticardiolipin antibodies. However, their pathogenic role has been questioned and protein S deficiency is currently considered to be an epiphenomenon in arterial stroke. Other common causes of ischemic stroke in AIDS patients are opportunistic infections of the CNS, such as toxoplasmosis, cryptococcal meningitis, and tuberculosis.

Treatment with protease inhibitors has been associated with premature atherosclerotic vascular disease[7] and an increased risk of myocardial infarction and stroke.[8] The Data Collection on Adverse Events of Anti-HIV Drugs Study found that the incidence of myocardial infarction increased by 26%, per year of exposure to HAART.[9] The increased risk of myocardial infarction may be partly explained by dyslipidemia.[10] No evidence of such an association for non-nucleoside reverse-transcriptase inhibitors has been found yet.

HIV infection may also predispose to cerebral infarction by means of a HIV-induced vasculopathy. Several facts support this hypothesis. Cerebrovascular hemodynamic function is impaired in HIV-infected patients, and evidence of abnormal vasomotor reactivity has been observed by transcranial Doppler.[11] An independent association of HIV infection with carotid artery intima-media thickness may exist.[12] The Edinburgh HIV autopsy cohort[13] described the existence of an HIV nonvasculitic vasculopathy characterized by small-vessel thickening, perivascular space dilatation, cortical rarefaction, pigment deposition, vessel wall mineralization, and perivascular inflammatory cell infiltrates. In the Cape Town Stroke Registry,[6] 20% of HIV-infected patients had clinical evidence of HIV-associated vasculopathy. HIV vasculopathy may manifest either extracranially (carotid artery occlusion or significant stenosis) or intracranially (medium-vessel occlusion with or without fusiform aneurysmal dilatation, stenosis, and vessel caliber variation).[14] Patients with extracranial vasculopathy usually have preserved CD4 counts, suggesting that this entity could occur as a consequence of an immunocompetent vasculitis. A cerebral vasculopathy with aneurysm formation has been described in HIV-infected young patients.[15]

Patients infected with HIV are at increased risk for the development of thrombosis. Cerebral venous and dural

Table 2: Etiologies and mechanism of AIDS-related stroke

1. **Ischemic stroke**
   - HIV-associated vasculopathy
     - Intracranial vasculopathy: aneurysmal and nonaneurysmal disease
     - Extracranial vasculopathy: aneurysmal and nonaneurysmal disease
   - Vasculitis-related opportunistic infections
     - Tuberculous meningitis
     - Systemic Mycobacterium avium intracellulare infection
     - Meningovascular syphilis
     - Varicella-zoster vasculitis
     - Cytomegalovirus vasculopathy
     - Herpes simplex virus
     - CNS mycosis:
       - Disseminated candidiasis
       - Cryptococcal meningitis
       - Aspergillosis
       - Mucormycosis
   - Cardioembolic stroke
     - Dilated cardiomyopathy
     - Rheumatic valvular disease
     - Nonbacterial thrombotic endocarditis
     - Infective (bacterial) endocarditis
     - HIV myocarditis
   - Thrombophilia and coagulopathy
     - Anticardiolipin antibodies
     - Positive lupus anticoagulant
     - Protein S deficiency
     - Disseminated intravascular coagulation
     - Associated conditions
       - Dehydration
       - Ulcerative colitis
       - Necrotizing enterocolitis
   - Others: CNS lymphoma, cerebral toxoplasmosis, hepatitis B antigenemia, heroin and other drug-related stroke
2. **Hemorrhagic stroke**
   - Cocaine and drug related-stroke
   - Basal ganglia hematoma secondary to hypertension
   - Subarachnoid hemorrhage due to rupture of infectious fusiform aneurysm

sinus thromboses have been reported in HIV infection.[16-22] In a study from India, such thromboses were observed in 4.4% of patients who had neurological symptoms due to the direct effects of HIV-1.[16] Acquired deficiency of proteins C and S in advanced AIDS,[17-19] coexisting infection with CMV[20] or varicella-zoster,[21] and a hypercoagulable state complicating AIDS-associated nephrotic syndrome[22] have been described in AIDS-related intracranial venous sinus thrombosis. Brain magnetic resonance imaging (MRI) and angiogram may show extensive dural sinus thromboses of the sagittal and transverse sinuses and multiple cerebral hemorrhagic infarcts.

Intracranial hemorrhages, lobar and deep cerebral (basal ganglia) hematomas, and cerebellar hematomas can also occur in HIV patients.[23] Associated factors include cerebral toxoplasmosis, neurotuberculosis, thrombocytopenia, vasculitis, hypertension, and cocaine abuse.[23] Cases of primary angiitis of the CNS have been reported in HIV patients.[24]

Stroke and emergent viral diseases

Japanese encephalitis virus

Japanese encephalitis (JE) virus is the most common cause of endemic encephalitis in humans. Every year, JE affects more than 50,000 individuals and results in more than 15,000 deaths. The infection, originally identified in Japan, has spread throughout Indian subcontinent, China, and South East Asia in the last few decades.[25] JE virus is a member of the genus *Flavivirus* (family Flaviviridae), which is transmitted between wild and domestic birds and pigs by Culex mosquitoes.

An increased incidence of neurocysticercosis (NCC) has been observed in patients with JE in endemic areas in China and India.[26-28] Desai *et al*. found that among the 163 confirmed cases of JE, 37.42% had coexistent NCC.[26] In another recent study from India, patients with JE had a significantly higher prevalence of NCC as compared with control subjects (19.3% vs 1.04%).[27] Both JE and NCC have some sociodemographic and ecologic factors in common; for example, pigs act as the amplifying host in JE and are the intermediate host in NCC. A significantly higher proportion of abnormal CT scans and more abnormal findings on MR imaging are observed in coinfection. JE lesions in coinfection are usually bilateral and asymmetrical; the more severe lesions are observed on the side harboring a solitary cyst of NCC, with edema on the side bearing the greater number of cysts or lodging the degenerating cyst.[29,30] Coinfections of NCC and JE are significantly more common in children and young adults and may result in poor neurological outcome and a increased risk of death from JE.[26]

Most JE infections are asymptomatic or produce only a mild flu-like illness that resolves within 1 week. Meningoencephalitis is a serious complication. Patients may present with a reduced level of consciousness, fever, headache, delirium, and seizures.[25] Coma, parkinsonian features, dystonia, and stroke-like symptoms are potential neurological complications.[31-33] Although adult patients with JE have a higher mortality rate in the acute stage, the long-term outcome seems to be better in adults as compared with children.[25,33]

Acute hemiplegia,[34] left hemispatial neglect[35] during the prodromal phase or as an initial symptom of JE, acute tetraplegia, and cerebral hemorrhage[36] during the course of JE have all been described. Brain CT abnormalities can be found in about 50% of patients and include thalamic, midbrain, and basal ganglia low-density areas, and cerebral edema. MRI is more sensitive and often reveals asymmetrical bilateral hemorrhagic lesions of the thalamus and T2-weighted signal changes in the

basal ganglia, midbrain, substantia nigra, pons, cerebral cortex, subcortical white mater, and/or cerebellum.[37] Single photon emission computed tomography (SPECT) studies carried during the acute stage have shown a marked decrease in cerebral perfusion in the affected hemisphere and hyperperfusion of the thalamus and putamen.[35,38]

Diagnosis can be made through virus isolation, polymerase chain reaction (PCR), and the detection of a four-fold increase in specific IgM by means of enzyme-linked immunoabsorbent (ELISA) technique. Lymphocytic pleocytosis is common in the cerebrospinal fluid (CSF).

There is currently no specific treatment for JE. Management of ischemic complications involves supportive care, with measures for the control of seizures and intracranial pressure. Corticosteroids have shown no benefit in JE.[39] Inactivated attenuated vaccine is used to protect swine against the virus.

Dengue hemorrhagic fever

Dengue virus is a Flavivirus transmitted by the bite of the mosquito *Aedes aegypti*. Dengue affects more than 100 million people worldwide each year. Additionally, 2.5 billion people are at risk of contracting the infection in tropical countries.[40]

Most infected patients present with influenza-like symptoms: high fever, headache, and myalgias. Four dengue virus serotypes have been associated with neurological complications. Acute encephalitis, Guillain-Barre syndrome, and Bell's palsy have been described during the acute infection.[41] A decreased level of consciousness and seizures can occur during acute encephalopathy.[42] Transverse myelitis and peripheral nerve palsies have been reported during the postinfectious stage. Brain MRI may show areas of hyperintensity in T2 sequences in the cerebral peduncle, lentiform nuclei, and internal capsule on both sides of the brain.[43] Diagnosis is based on epidemiological data (eg, increased incidence during the monsoon or rainy periods in endemic areas), a clinical picture consistent with dengue infection (eg, break-bone fever and hemorrhagic manifestations), and a positive IgM for dengue.

Dengue hemorrhagic fever is the most severe form of the disease; thrombocytopenia, increased vascular permeability, and hemorrhagic diathesis may provoke systemic complications and shock. Encephalopathy is a severe complication and may occur as a consequence of intracranial hemorrhage,[44] brain edema, hyponatremia, cerebral anoxia, fulminant hepatic failure with portosystemic encephalopathy, microcapillary hemorrhage, or release of toxic products.

Other viral hemorrhagic fevers

Most viral hemorrhagic fevers are transmitted by mosquitoes, ticks, or rodents. Bunyaviridae (i.e., Rift valley virus, Congo-Crimea virus, Hantaan virus) cause viral hemorrhagic fevers in Africa and Asia. In Asia, some flaviviruses are endemic (eg, Omsk hemorrhagic fever virus, Alkhurma hemorrhagic fever virus, Kyasanur forest disease virus). Ebola, Marburg (Filoviridae), and Lassa (Arenaviridae) virus are other endemic viruses in Africa.[2]

Korean hemorrhagic fever is one of a group of very severe, clinically similar illnesses known as hemorrhagic fever with renal syndrome. Korean hemorrhagic fever is caused by the Hantaan virus, a rodent-borne hantavirus that is widely distributed throughout eastern Asia, particularly in China, Russia, and the Korean peninsula. The possible presence of hantavirus infections in the human population of India, presenting both as asymptomatic and symptomatic infections, has been suggested.[45]

Viral hemorrhagic fevers can cause systemic and intracranial hemorrhages by several mechanisms: increased vascular permeability, platelet dysfunction, thrombocytopenia, and disseminated intravascular coagulation.[46] Pathological studies of the brain have shown the presence of small brain hemorrhages associated with capillary dilatation and extravasations of red blood cells.[47]

Diagnosis can be confirmed by viral isolation, PCR, and identification of antibodies in the CSF or serum. Treatment is supportive. Ribavirin (30 mg/kg loading dose, followed by 15 mg/kg every 6 h for 4 days and then 7.5 mg/kg every 8 h for 6 days) may be useful in arenavirus and bunyavirus infection; however, there is no proven efficacy in flavivirus infection.[48]

West Nile virus

West Nile Virus (WNV) is a Flavivirus that is transmitted to humans through infected Culex mosquitoes. Transmission is also possible in utero and through blood transfusions, organ transplantation and, probably, breast-feeding.[49] Several epidemics have occurred in United States, South Africa, and Israel. Most WNV infections cause only a mild illness, called West Nile fever, with malaise, headache, myalgia, anorexia, and rash.

Neurological complications can occur in 1 in 150 infected people. Encephalitis, meningitis, anterior horn cell discease, myelitis, optic neuritis, ataxia, persistent movement disorders, and cranial nerve abnormalities have been described.[49] Stroke associated with CNS vasculitis following WNV infection[50,51] and retinal artery occlusive vasculitis[52,53] have been described in

children and adults. Persons with diabetes and history of alcohol abuse and older persons are at increased risk of developing ischemic neurological complications. When WNV encephalitis occurs in those who have a previous history of stroke or are immunosuppressed there is an increased risk of death; similarly, those patients who require mechanical ventilation also have higher mortality.[54]

Varicella-zoster virus

A) Post-varicella childhood cerebral infarction: Varicella-zoster virus (VZV) has been identified as a stroke risk factor in 1- to 10-year-old children.[55] In a prospective study, one-third of children with arterial ischemic stroke had a varicella virus infection in the preceding year.[56] Varicella-associated arterial ischemic stroke has been estimated to occur in 1 in 15,000 children. Children with post-varicella stroke have an increased frequency of hemiparesis, basal ganglia and anterior circulation infarctions, and stenosis of the proximal region of the major cerebral arteries.

Cerebral vessel imaging usually reveals unilateral stenosing arteriopathy affecting the distal internal carotid artery (ICA) and proximal segments of the anterior cerebral artery (ACA) and middle cerebral artery (MCA). MRI may show infarctions within the vascular territory of the lenticulostriate branches (i.e., in the basal ganglia and internal capsule).[57]

Intraneuronal migration of varicella-zoster virus from the trigeminal ganglion, along the trigeminal nerve, to the cerebral arteries has been postulated as a pathogenic mechanism. The virus may cause vessel-wall inflammation, large-vessel granulomatous angiitis, and secondary thrombosis.

Dystonia is a severe late complication of varicella-related basal ganglia infarction.[58] Vascular stenosis usually takes a monophasic course, and is followed by stenosis regression. A clinical recurrence has been observed in a quarter of cases and is associated with progressive arteriopathy.[58] Stroke rarely recurs if antithrombotic prophylaxis is given; however, the efficacy and optimal duration of antithrombotic therapy is unknown. There is no proven benefit with antiviral drugs or corticoids.

B) Varicella-zoster virus and HIV coinfection: VZV infection can be seen in association with HIV infection and may then have a different spectrum of clinical features from that seen in non-inmunodepressed patients: VZV cerebral vasculopathy usually occurs late in the course of the infection, is seen in patients with marked CD4+ depletion, and has greater mortality. Cases of ischemic stroke have been reported in children with AIDS and prolonged VZV skin infection; radiologic and histopathologic evidence of CNS vasculitis has been observed.[59] The syndrome of herpes zoster ophthalmicus followed several weeks later by a contralateral hemiplegia has also been reported in HIV patients.[60] Large artery vasculopathy can provoke a hemispheric stroke secondary to cerebral granulomatous angiitis. Stroke can also occur without clinical history of zoster dermatitis in HIV-infected patients.[61]

Tuberculosis

Neurological involvement accounts for around 3% of extrapulmonary tuberculosis cases and is more common in children and immunosuppressed patients. Tuberculous meningitis (TBM) results from the hematogenous dissemination of *Mycobacterium tuberculosis* from the lungs to the brain. In the brain parenchyma, *M tuberculosis* induces an inflammatory response and formation of small tubercles called Rich's foci. The neurological complications of TBM include cranial neuropathies, hydrocephalus, cerebral and spinal arachnoiditis, myelopathy, and stroke.[62]

Dissemination is believed to occur early during infection, before the development of adaptive immunity. Polymorphisms in the toll-like receptor 2 (TLR2) gene may influence bacterial dissemination and the development of TBM. TLR2 mediates recognition of *M tuberculosis* and initiates the innate immune response to infection. TLR2 genotype 597CC has been associated with susceptibility to TBM and the severity of the neurological symptoms.[63]

Stroke is a severe complication of TBM and delay in diagnosis and treatment is related to a poor outcome.[64] Cerebral infarctions are frequently associated with other neurological complications, such as hydrocephalus and seizures.[65] The frequency of cerebral infarctions in TBM varies between 10 and 47%.[64-66] A vasculitis involving the perforating vessels of the brain is a characteristic hallmark of TBM-associated stroke. Small, medium, and large arteries of the anterior circulation can be involved. Lenticulostriate branches of the MCA are frequently affected. Most of infarctions are located in the basal ganglia, internal capsule, and thalamus. Posterior circulation infarctions are less common. Tuberculous infiltration and occlusion of venous sinus can provoke hemorrhagic infarction.[67] Although intracranial hemorrhages are uncommon, the leptomeningeal exudate can produce changes in the artery wall with formation of mycotic aneurysms that may rupture. Tuberculomas may also induce vascular lesions and intraparenchymal hemorrhages.[68] Intraventricular hemorrhages due to a ruptured posterior inferior cerebellar artery aneurysm has also been described.[69]

Vessel constriction, periarteritis, necrotizing panarteritis

of the circle of Willis, and secondary thrombosis can occur as exudative basal meningitis progresses.[70]

Several mechanisms have been proposed to explain stroke in TBM: 1) A necrotizing panarteritis of the vessels of the circle of Willis can occur as a result of a chronic exudative basal meningitis; 2) segmental constriction and spasm of vessels located at the base of the brain can provoke thrombosis and vasculitis; and 3) in some cases, hydrocephalus and dilated ventricles may stretch compromised brain vessels and possibly aggravate ischemia.[71,72]

Low-grade fever, nuchal rigidity, somnolence, cranial nerve palsy, hydrocephalus, and seizures can occur in TBM. A clinical study from Mumbai showed that the presence of deep coma may be an independent predictor of mortality in TBM.[73] Stroke symptoms manifest as a sudden onset of focal motor weakness. The CSF may reveal a lymphocytic pleocytosis, elevated proteins, low glucose, and normal chlorine levels. A positive PCR for tuberculosis can help to establish the diagnosis, although it may be positive in only 50% of cases. Brain CT or MRI may show ischemic and/or hemorrhagic areas, hydrocephalus, and arachnoiditis.[71,72] Segmental narrowing of the basal arteries can be found on angiography.

Morbidity and mortality remains high even with optimal use of chemotherapy. Adjunctive treatment with corticoids improves survival in patients over 14 years of age,[74] although it probably does not prevent severe disability. Dexamethasone 16 to 32 mg/day may ameliorate angiitis-related symptoms. Corticoids may also affect the outcome by reducing hydrocephalus and preventing infarction.[75] Mortality rates for cases with advanced disease are higher than 50%.

Leptospirosis

Leptospirosis is an infectious disease caused by the spirochete *Leptospira interrogans*. The geographical distribution includes many tropical areas in Southern Asia and South America. Humans acquire the disease through contact with urine from infected animals and/or by direct contact of the skin or mucous membranes with contaminated water or soil.[76] Floods may change the environment drastically, making it conducive for transmission of infection. Outbreaks of leptospirosis in flooded villages after a cyclone are common in Central America and Asia.[77]

A biphasic evolution is characteristic of leptospira infection. During the first stage, flu-like symptoms (fever, headache, nausea, myalgia, and lymphadenopathy) can occur. Renal and hepatic symptoms and persistent fever appear in the second stage of the disease. Weil's syndrome (jaundice, renal and hepatic failure, myocarditis, and a bleeding diathesis) is a severe form of the disease. Neurological involvement in leptospirosis can present as meningitis, aseptic encephalitis, inflammatory myelopathy, Guillain-Barre syndrome, and stroke.[78] Altered mental status and renal and pulmonary insufficiency are significant predictors of death.

A few patients may develop a Moya moya-like progressive intracranial arteriopathy after infection with *Leptospira interrogans* serovar. *pomona*.[79] In these cases, cerebral panarteritis involves the main trunks of larger arteries at the base of the brain, and watershed and anterior circulation infarctions may occur.[80] Intracranial hemorrhage due to severe thrombocytopenia is a rare complication of Weil's syndrome.[81]

The differential diagnoses should include viral hemorrhagic fevers and dengue fever. The diagnosis can be made through the isolation of leptospires from urine or blood. They can be identified in the blood sample by their characteristic morphology and 'paddle wheel' motility. Detection of IgM specific antibodies and the microagglutination test can be useful in the diagnosis. Brain MRI and MRI-angiography may show ischemic and hemorrhagic areas. A Moya-moya pattern on angiography, with a rich network of cerebral artery collaterals, can be detected in the angiography. The infection can be treated with several types of antibiotics, including penicillin, doxycycline, and aminoglycosides.

Mycosis of the CNS

Fungal infections are relatively frequent in the tropics. Systemic mycosis are more common in immunocompromised hosts (eg, following organ transplantation, cancer, chemotherapy, chronic use of corticoids, and AIDS), pregnancy, and in patients who have undergone cardiovascular surgery. CNS mycosis can manifest as chronic meningitis, acute meningoencephalitis, brain abscess, and stroke.

In most of cases, fungi reach the CNS via hematogenous dissemination from the lungs, heart (mycotic endocarditis), or skin. Cerebrovascular complications of CNS mycosis are associated with large vessel vasculitis, direct vessel damage (occlusion) by invasion or embolization, and subarachnoid hemorrhage due to rupture of a mycotic aneurysm. Mycotic aneurysms may also be associated with intracerebral hemorrhages and these occur in distal branches of the intracranial arteries. The most common fungal infections will be briefly reviewed.

Coccidioides immitis, a dimorphic fungus commonly found in Central and South America, can provoke chronic meningitis. Tumor-like lesions, hydrocephalus, spinal arachnoiditis, and stroke caused by cerebral vasculitis are neurological complications of Coccidioides infection.[82]

Disseminated aspergillosis has been described in immunosuppressed patients (eg, those with severe neutropenia or AIDS), and in chronic systemic diseases (eg, tuberculosis, alcoholism, or cancer). *Aspergillus sp.* may cause multiple brain abscesses, cerebral thrombosis, intracranial mycotic aneurysms, and subarachnoid hemorrhages.[83,84] Mycotic aneurysms of the basilar artery following surgical interventions have been reported.[85] Sometimes, the diagnosis of aspergillosis is made at autopsy in patients presenting with subarachnoid hemorrhage.

Disseminated *Candida albicans* infection is common in premature babies. CNS candidiasis has also been described in adults. People at risk are drug users, neutropenic patients, and patients who have received prolonged antibiotic treatments after major surgery or traumatic brain injury. CNS candidiasis can provoke arteritis, subarachnoid hemorrhage, and multiple brain micro-abscesses.[86]

Cryptococcus neoformans meningitis is the second most common CNS infection in AIDS patients. Stroke due to vasculitis and occlusion of cerebral branches has been reported [Figure 2A and B].[66,87]

Fungal infections complicated with stroke have high mortality. Aggressive and early treatment should be initiated. Intravenous amphotericin, 5-fluocitosine, and endovenous fluconazole are first-line treatments. Antibiotherapy and surgery are therapeutic options for mycotic aneurysms.

Rhino-Orbital-Cerebral Mucormycosis

Rhino-orbital-cerebral mucormycosis (ROCM) is an acute, and often fatal, opportunistic necrotizing infection of the sinuses, orbit, and brain caused by *Zygomycetes sp*. ROCM usually develops in adolescents with type 1 diabetes mellitus who have poor glycemic control (with or without ketoacidosis), and in patients with malignant hematological disorders, chronic renal failure, or metabolic acidosis.[88] These patients usually present with unilateral orbital cellulitis and cavernous sinus syndrome. Headache, blurred vision, fever, painful ophthalmoplegia, proptosis, and cranial nerve involvement are common clinical findings.[89]

Cerebral infarcts and intracerebral hemorrhages have been reported in CNS *Zygomycetes* infection.[88-91] Cavernous sinus and carotid thrombosis may provoke a malignant cerebral infarction. Less frequently, a basilar artery thrombosis or a bilateral occipital infarction may occur. It is thought that accelerated thrombotic occlusion of the cavernous portion of the carotid artery may be due to mucormycosis-associated vasculopathy and diabetic vasculopathy. Massive subarachnoid hemorrhage following rupture of a mycotic aneurysm has also been reported.[90] Brain MRI may reveal bone destruction, vascular invasion, central hypointensity in the paranasal sinuses, an intracranial mass, and brain ischemia [Figure 3]. Patients who have altered sensorium, facial necrosis, unsuspected diabetes mellitus, and mucormycosis-associated malignant stroke at presentation have poor outcome.[89] Parenteral and local administration of amphotericin B and radical surgery, with early radical debridement, has been effective in reducing the mortality.

Cerebral Malaria

Malaria is a major public health problem in the tropics.

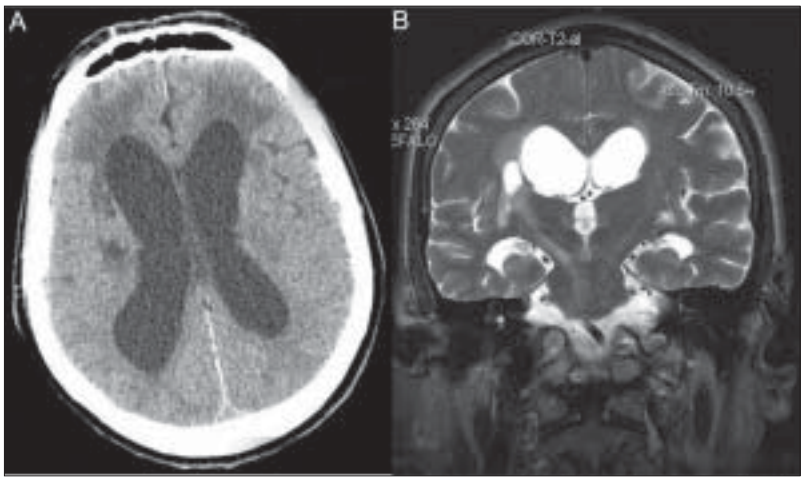

Figure 2: Ischemic stroke in a patient with *Cryptococcus neoformans* meningitis. CT scan (A) and brain MRI T2-weighted sequence (B)

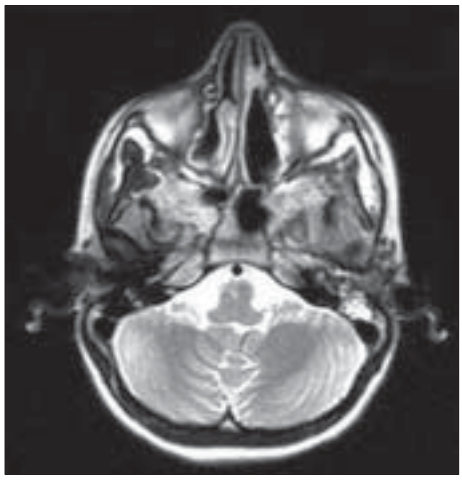

Figure 3: Brain MRI. Rhino-orbital-cerebral mucormycosis

More than 500 million of cases are reported each year, 25% in Southeast Asia and 70% in Africa.[92] Most of cases of cerebral malaria are due to *Plasmodium falciparum;* however, even *P vivax* may affect the CNS. Rarely, *P vivax* infection may present as cerebral malaria.[93]

Cerebral malaria occurs in around 2% of patients infected by *P falciparum* and is much more common in children. Child mortality due to cerebral malaria varies between 20 and 50%. In adults, populations at risk include pregnant women, immunodepressed patients, and nonimmune travelers exposed to *P falciparum*.[92]

The World Health Organization proposed a definition of cerebral malaria,[94] according to which other causes of encephalopathy (including acute bacterial meningitis or viral encephalitis, and toxic/ metabolic encephalopathy) should be ruled out. In a pathological study performed in Malawi, 25% of children diagnosed clinically as having cerebral malaria had other causes that explained their symptoms.[95]

The main pathological findings of cerebral malaria are diffuse cerebral edema, perivascular ring hemorrhages, white matter necrosis, parenchymal petechial hemorrhages, occlusion of brain vessels, and sequestration of infected erythrocytes in cortical and perforating arteries.[96,97]

Small infarcts of the cortex can occur due to blockage of capillaries by infected and noninfected erythrocytes that are packed within cerebral vessels. Sequestration may happen as a consequence of cytoadherence of infected red blood cells to endothelium via *P falciparum* surface antigens. The reduced erythrocyte deformability also favors a reduction of cerebral blood flow.[98]

In some cases, brain ischemia and neurological symptoms may revert after treatment. Nevertheless, several complicating factors such as seizures, severe anemia, hypoglycemia, hypovolemia, and acidosis may provoke an impairment of endothelial cells and cerebral microvasculature. As a consequence, increased vascular permeability, edema, necrosis of wall vessels, intravascular thrombosis, cerebral ischemia, and focal neurological deficits can occur.[99] The following factors may also provoke a raised intracranial pressure and brain swelling: the sequestration of red cells; the disruption of the blood-brain barrier; the presence of cytotoxic edema; and the increase of cerebral blood flow due to epilepsy, hyperthermia, or anemia.[100]

Patients usually present with a 2-3 day history of anorexia, fever, cough, nausea and vomiting, headache, muscle pain, and disorientation. In some cases, coma may be the first symptom of cerebral malaria. Delirium, seizures, brainstem signs (eg, changes in pupillary size and impairment of corneal and oculocephalic reflexes), and focal motor deficits (eg, hemiparesis and aphasia) may appear as the clinical picture worsens. Retinal abnormalities (eg, whitening of the macula or retinal hemorrhages) are common in children. Abnormal motor posturing (eg, opisthotonus or decorticate rigidity), deviation of conjugate gaze, status epilepticus, and death can occur in the most severe cases.[99,101,102] Concomitant systemic complications include severe hypoglycemia and anemia, metabolic acidosis, hyponatremia, CNS bacterial infections, renal insufficiency, and pulmonary edema.

The incidence of stroke in cerebral malaria is unknown. Ischemic and hemorrhagic stroke, cerebral venous thrombosis, and dural sinus thrombosis have been described as a consequence of a hypercoagulable state.[102,103] Neurological sequelae have been reported in around 10% of patients and include focal deficits (eg, hemiparesis, ataxia, and tremor), epilepsy, cognitive dysfunction, and visual and language disturbances.[104,105]

The CT scan findings may vary; there may be: 1) a normal CT scan, which is associated with the more 'benign' form of cerebral malaria, a good prognosis, and full recovery; 2) diffuse cerebral edema; 3) bilateral thalamic and cerebellar hypoattenuation; 4) diffuse cerebral edema associated with bilateral thalamic hypoattenuation; 5) small cortical infarctions; and 6) areas of petechial hemorrhages. MRI studies have shown impairment of the splenius of the corpus callosum and centrum semiovale, cerebellar and thalamic infarctions, and isolated ischemic lesions of the pons and medulla.[103-109]

Patients should be treated early with antimalarial drugs, such as cinchona alkaloids (eg, quinidine or quinine) or artemisinin derivatives (eg, artesunate or artemether). Quinine dihydrochloride (loading dose: 20 mg/kg over

4 h; maximum dose: 600 mg; and maintenance dose: 10 mg/kg every 8 h) is commonly used. The loading dose is associated with faster clearance of parasitemia and resolution of the impaired state of consciousness. Side effects of quinine include hyperinsulinemic hypoglycemia, tinnitus, high-tone deafness, and color aberrations. High doses can induce uterine contractions in women.[98]

Artemisinin derivatives reduce parasitemia faster and diminish mortality in adults with severe malaria, and therefore may be preferable in patients with a parasite count >10%. In the South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT), parenteral artesunate was associated with a considerably lower mortality than quinine. Artesunate should constitute first-line treatment for severe malaria in South East Asia since these patients may have quinine-resistant malaria.[110] Artesunate is also the recommended treatment for severe malaria in low-transmission areas and in the second and third trimesters of pregnancy.

Trials comparing artemether with quinine in children with severe malaria have not demonstrated convincing evidence of a mortality advantage for artemether. Although parasitemia clearance and coma recovery occurred earlier in artemether-treated patients, mortality was similar in those treated with quinine or artemether.[111]

Artemisins are generally well tolerated. Artemisins should be used in malarial stroke patients with associated cardiac conditions since quinine is proarrhythmogenic. The dose used in cerebral malaria is as follows: 1) artesunate, 2.4 mg/kg given intravenously at 0, 12, and 24 h, and then daily; 2) artemether, 3.2 mg/kg given intramuscularly as loading dose, followed by 1.6 mg/kg intramuscularly daily to a total of 640 mg. Artemisins should be followed by doxycycline (100 mg daily for 7 days) or artemether-lumefantrine.[112]

Corticoids are deleterious in cerebral malaria. A clinical trial found that dexamethasone therapy increased the stupor period as well as the risk of infection and gastrointestinal bleeding.[113] Supportive care, control of seizures and hypoglycemia, ventilatory support, and blood transfusion may be necessary.[114]

Neurocysticercosis

Cysticercosis, or tapeworm infection, is the most common CNS parasitic infection worldwide. *Taenia solium* infestation is endemic in Africa, Asia, and South America, and NCC remains a major public health problem in developing countries. Neurological symptoms include seizures; cognitive dysfunction (secondary to hydrocephalus, chronic meningitis, and/or raised intracranial pressure); and focal deficits caused by the compressive effect of the cysticerci, arachnoiditis, or hydrocephalus.[115] Common clinical-topographical syndromes include chronic meningitis, parenchymal cysticercosis, subarachnoid cysticercosis, and intraventricular cysticercosis.

The main factors that influence the appearance and severity of neurological symptoms are: a) the number, type, size, viability, and location of the cysts; b) the intensity of the immune reaction of the host to the parasite in the CNS tissue; and c) the degree of obstruction to the CSF. Arachnoiditis, granulomas, focal cerebral edema and/or arteritis can occur as a result of the inflammatory process.[115]

Ischemic and hemorrhagic lesions can be observed in NCC and are associated with cerebral vasculitis. Cerebrovascular complications include transient ischemic attacks, ischemic stroke (lacunar infarctions in the territory of the lenticulostriate branches and, less commonly, large artery infarctions), and intracranial hemorrhages. The frequency of cerebral infarction associated with NCC varies between 2 and 14%.[116-118] In endemic areas, it is estimated that 2.5-10% of strokes in young and middle-aged patients are associated with NCC.[119,120]

Pathological studies have shown the presence of an inflammatory arteriopathy in the vessels neighboring the parasites located in the subarachnoid space, near the arteries that form the circle of Willis.[119] Cysticercotic angiitis predominantly affects small- and middle-sized cerebral arteries. Angiographic studies have shown evidence of cerebral arteritis in middle-sized arteries in around 50% of patients affected by subarachnoid cysticercosis.[121] Less commonly, large infarctions can occur due to occlusion of a main trunk of an intracranial artery. Cysticercal chronic basal arachnoiditis with infarcts may mimic CNS tuberculosis in endemic areas.[122] Focal arteritis secondary to parenchymal cysticercosis is uncommon; it may appear as a small-vessel disease and an isolated lacunar infarction.

Subarachnoid NCC is a more complex form of the disease; occlusion of both perforating arteries and large arteries (MCA and carotid artery) can occur as a result of endarteritis. Lacunar infarction is the most frequent stroke subtype associated to subarachnoid cysticercosis. Several lacunar syndromes have been described, of which pure hemimotor syndrome and ataxia/hemiparesis syndrome are the most frequent.[123,124] Cysticercosis of the subarachnoid space of the convexity is probably the most common form of subarachnoid NCC in endemic

countries and may appear as a solitary cyst or as multiple cysts. The majority of these patients develop neither hydrocephalus nor cerebral infarction. However, seizures are common. This subtype of NCC may provoke an inflammatory reaction around middle- and large-sized arteries, leading to their occlusion. Bilateral occlusion of both MCAs has also been reported.[125]

Patients affected by NCC of the sylvian cisterns may present with seizures, stroke, or raised intracranial pressure syndrome. The occlusion of the main trunk or branches of the MCA can occur as a consequence of severe arteritis due to large racemose cysts or arachnoiditis. Stroke has been described in this type of patient during treatment with praziquantel or albendazole. The destruction of subarachnoid cysts during cysticidal therapy may provoke a change in the wall of the leptomeningeal vessels and lead to their occlusion. Stroke of the MCA associated with treatment with albendazole or praziquantel[126] usually occurs in patients with severe vasculitis and arachnoiditis.

Cysticercosis of the basal cisterns around the brainstem is also common. Focal deficits can occur as a consequence of chronic compressive arachnoiditis. Some patients may have a hemiparesis as the initial presenting complaint due to arteritis of the circumferential arteries of the brainstem.

Hemorrhagic stroke associated with NCC includes intracystic hemorrhage, cerebral hemorrhage secondary to an inflammatory arteritis of the small perforating branches, and subarachnoid hemorrhage secondary to the rupture of a mycotic aneurysm.[127] Rupture of a concomitant aneurysm can be favored by the presence of a severe inflammatory process in the thickened leptomeninges around the dilated vessel.[127]

Clinical, radiological, and CSF data should be interpreted together when diagnosing cysticercosis-related stroke. The major diagnostic criteria for NCC include: 1) the presence of suggestive lesions on brain CT or MRI (cysts with well-defined scolices, enhanced ring lesions, and calcified cysticerci), positive antibodies in blood (immunoblot technique), and the resolution of lesions after treatment with cysticidal drugs.[128] CSF analysis may show pleocytosis, raised levels of proteins, and normal or decreased levels of glucose and eosinophils. The ELISA test can detect *T. solium* antibodies in the CSF.

Neuroimaging findings are highly variable and can help to differentiate between ischemic and hemorrhagic strokes. Viable cysts with scolices, variable degrees of edema and contrast enhancement around intraparenchymal cysts, subarachnoid cysticerci, intraventricular cysts, parenchymal calcifications, hydrocephalus, leptomeningeal enhancement, and ischemic and hemorrhagic areas can be observed on MRI. Conventional angiography, MRI-angiography, and transcranial Doppler are useful tools to evaluate cysticercosis-related arteritis.[129]

Viable cysts can be treated with albendazole (15-30 mg/day for 8-15 days) or praziquantel (50 mg/kg/day for 15 days). A single dose of praziquantel (100 mg/kg) seems to be sufficient to treat single lesions. Dexamethasone (16-32 mg/day) should be used to reduce inflammatory reaction before and during cysticidal therapy and to diminish the risk of ischemic events in cases of subarachnoid NCC.[115] Resolution of arterial stenosis in a patient with periarterial NCC who was treated with oral prednisone has been described.[130]

American Trypanosomiasis

American trypanosomiasis, also called Chagas' disease (CD), is an infection caused by the flagellate protozoan *Trypanosoma cruzi*.[131] Chagas' disease is a major health problem in South America and, potentially, an emergent medical problem in the United States and Western Europe. It is estimated that up to 8% of the population in South American countries are seropositive for *T. cruzi*. Around 20 million people have chronic *T. cruzi* infection, and the disease causes approximately 50,000 deaths each year.[132]

The main risk factor for the transmission of CD is the presence of triatomine bugs (Reduviidae) infected by *T. cruzi* in human dwellings. Several sylvatic vertebrates can function as natural reservoirs. The infection is acquired by the transmission of *T cruzi* via the bite of the kissing bug. The entry of trypanosome through the skin or mucous membrane is facilitated by the scratching of the bite by the sleeping victim. Other less common modes of transmission are via blood transfusion, transplantation of infected organs, and ingestion of contaminated food or drinks.[131]

Acute *T cruzi* infection occurs most often in childhood. It is usually asymptomatic but can present with fever, an indurated cutaneous lesion called 'chagoma,' lymphadenopathy, and hepatosplenomegaly. Most infected persons remain asymptomatic in a latent or subclinical stage of variable duration called indeterminate CD. Only CD antibodies can be detected in this indeterminate form of the disease. Serologic diagnosis is by the detection of indirect fluorescent antibodies (immunofluorescence test), indirect hemagglutination test, and ELISA.

Chronic cardiomyopathy is the most common clinical

form of CD. It affects about 30% of patients, and its symptoms begin, on average, 10-30 years after the initial infection. chagasic cardiomyopathy is characterized by heart failure and progressive cardiac enlargement, cardiac arrhythmias (sinus node dysfunction, intraventricular conduction system abnormalities, atrial fibrillation, and ventricular arrhythmias), sudden death due to cardiac arrest, and peripheral thromboembolism.[133] Several factors, including parasite persistence, inflammation, selective destruction of postganglionic parasympathetic neurons, and alterations of the host's immune system have been implicated in the progressive heart damage caused by *T cruzi*.

Chagasic cardiomyopathy is independently associated with ischemic stroke. Cardiac arrhythmias, congestive heart failure, apical aneurysm, and mural thrombus are potential embolic sources that partially explain the genesis of chagasic stroke.[134] In central Brazil, around 20% of stroke patients are seropositive for American trypanosomiasis, and the diagnosis of CD may be established after stroke in more than 40% of chagasic patients.[135] More than 20% of CD stroke patients have a history of a previous stroke. The MCA territory is the most common recipient site for cardioembolism: this has been observed in at least 70% of chagasic patients [Figure 4].

The apical region of the left ventricle is a critical region in the chagasic heart, where aneurysm, thrombus, or both, occur with high frequency. The frequency of apical aneurysm in CD stroke patients studied by echocardiography is around 37%.[135] However, not all stroke chagasic patients have a severe cardiomyopathy. Stroke may be the first manifestation of CD in patients with mild or undetected systolic dysfunction. Chagasic patients with no clinical evidence of heart failure or threatening arrhythmia are also at risk of stroke.[135]

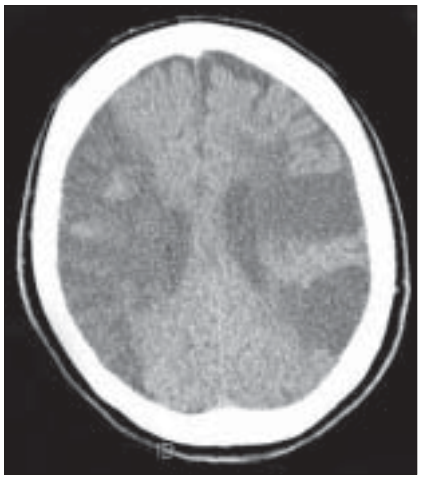

Figure 4: Multiple ischemic areas in a patient with American trypanosomiasis

The effectiveness of trypanocidal drugs (eg, nifurtimox and benznidazole) during the indeterminate and chronic stages of CD remains unclear. Although recent clinical trials have reported high rates of parasitologic cure in children with early chronic *T cruzi* infection,[136] no specific therapy has so far been found to be effective in the chronic stage of the disease.

Management of chronic chagasic cardiomyopathy involves the use of antiarrhythmic drugs and diuretics. Sick sinus syndrome, ventricular arrhythmias, and severe atrioventricular conduction blocks may require pacemaker or automatic cardiodefibrillator insertion. Almost 10% of CD stroke patients are on pacemaker.

Secondary prevention with oral anticoagulation should be considered in CD patients with stroke and heart failure, atrial fibrillation, mural thrombus, or segmental lesions (eg, apical aneurysm).[131]

Gnathostomiasis

Gnathostoma spinigerum is a nematode endemic in Mexico, South America, and Southern Asia (Korea, Thailand, China, and Japan). The adult worm lives in the host's (usually cat or dog) stomach. The primary intermediate host is the freshwater copepod of the genus Cyclops, while the secondary intermediate hosts are pigs, ducks, fish, and water snakes. Human beings are infected by eating raw or undercooked fish or poultry and by drinking copepod-contaminated freshwater. Once ingested, the larvae cross the intestinal wall and migrate to the subcutaneous tissues. Intermittent, painful, subcutaneous swellings are a common symptom.

Neurological complications include seizures, headache, hydrocephalus, transverse myelitis, painful radiculomyelitis, and hemorrhagic strokes. *G. spinigerium* is a frequent cause of eosinophilic meningitis. The immunological response of the host produces a leptomeningeal inflammation. Transverse myelitis can occur as a consequence of migration across the spinal cord.[137]

G. spinigerum infestation is a cause of hemorrhagic stroke in Asia. The migration of the larvae through the cerebral parenchyma leaves hemorrhagic and necrotic tracts surrounded by inflammatory infiltrates.[138,139] Intracranial hemorrhages occur in 15-30% of patients with cerebral involvement. In Thailand, around 16% of subarachnoid hemorrhages in children and adolescents are due to *G spinigerum* infection.[140]

Eosinophilic meningitis with a xanthochromic CSF is the hallmark of the disease. The CSF, in addition to xanthochromia, also shows pleocytosis (white cell count

of 500-2,000/cu mm) with a predominance of eosinophils (20-70%), raised proteins (>100 mg/dl), and normal levels of glucose.

A serologic test using the immunoblotting technique with a polypeptide marker weight of 24 kDa of *G spinigerum* has nearly 100% specificity. CSF and serum are usually positive for *G. spinigerum* as per immunodiagnosis. Brain MRI may show hydrocephalus, brain swelling and periventricular edema, leptomeningeal gadolinium enhancement, and the presence of multiple hemorrhagic tracts in the brain parenchyma.[141,142] Recovery of the parasite from the tissue provides the definitive diagnosis.

There is no specific treatment for neurognathostomiasis. Cutaneous gnathostomiasis can be treated with albendazole. The use of albendazole can exacerbate neurological symptoms as a result of larval death within the CNS. Corticoids (prednisolone, 1 mg/kg/day or dexamethasone, 32 mg/day) have been used to treat brain edema and intracranial pressure. Prognosis depends on the severity and extension of the intracranial hemorrhage.

Conclusion

There are some specific causes of stroke in developing countries. Endemic tropical diseases may be responsible for a relatively high percentage of strokes in otherwise young and healthy people. Infectious diseases should be included in the differential diagnoses of stroke. Prevention and treatment are important in the control of infectious diseases in the tropics.

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