

Infectious Causes of Stroke

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Overview

Stroke is the second-leading cause of death globally, accounting for approximately 12 percent of total deaths worldwide (1). In the United States, stroke ranks as the 5th leading cause of death, killing nearly 133,000 people a year, and is a leading cause of serious long-term disability (2). Established risk factors include hypertension, hyperlipidemia, smoking, obesity, and diabetes, though recent studies have shown that infection confers additional risk (3). The growing burden of stroke is concerning, particularly in low and lower middle income regions, where infection may play a larger role. Recent studies have shed light on the complex interactions between infection and stroke, including the direct stroke risk associated with a variety of neurotropic infections including several viruses, fungi, bacteria, and parasites. In patients with infective endocarditis, septic cerebral embolism is a significant risk factor for embolic strokes. Evidence also suggests that systemic infection may trigger acute stroke in patients with vascular risk factors.

Primary CNS infections:

Many CNS infections can directly cause stroke, including bacterial (i.e. syphilis and tuberculosis), fungal (i.e. cryptococcus, aspergillus, mucormycosis), parasitic (neurocysticercosis), and numerous viruses (3) (Table 1 and 2).

| Infectious causes | | Ischaemic | Haemorrhagic |
|---|--|----------------------------|--------------|
| Preceding or concomitant systemic infection, outside the CNS | Influenza Chlamydia pneumoniae Helicobacter pylori Porphyromonas gingivalis | | |
| Preceding or concomitant infection, contiguous with the CNS | Streptococcus pneumoniae sinusitis Haemophilus influenzae sinusitis Moraxella catarrhalis sinusitis Aspergillus fumigatus sinusitis Mucormycosis sinusitis | | |
| Total non-specific infectious burden | More than one current or previous systemic infection | | |
| Vasculitis and mycotic aneurysm | HIV Varicella zoster virus Syphilis Neuroborreliosis Epstein-Barr virus Cytomegalovirus Tuberculosis Neurobrucellosis | | |
| Vascular remodeling | HIV Syphilis | | |
| Promotion of a hypercoagulable state | Hepatitis C | | |
| Infectious endocarditis | Staphylococcus aureus Coagulase-negative staphylococci Viridians group streptococci Streptococcus bovis Enterococci HACEK bacteria Escherichia coli Klebsiella pneumoniae | | |
| Cardiogenic emboli to the cerebral vasculature from dilated cardiomyopathy | Chagas disease | | |
| HACEK=Haemophilus parainfluenzae, Haemophilus aphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella kingii. | | | |
| | | Bacteria | |
| | | Staphylococcus aureus | ✓ |
| | | Streptococcus pneumoniae | ✓ |
| | | Streptococcus viridans | ✓ |
| | | Streptococcus bovis | ✓ |
| | | Haemophilus influenzae | ✓ |
| | | Haemophilus parainfluenzae | -- |
| | | Neisseria meningitidis | ✓ |
| | | Listeria monocytogenes | ✓ |
| | | Pseudomonas aeruginosa | -- |
| | | Chlamydia pneumoniae | ✓ |
| | | Mycobacterium tuberculosis | ✓ |
| | | Treponema pallidum | ✓ |
| | | Bruceella sp | ✓ |
| | | Borrelia sp | ✓ |
| | | Nocardia asteroides | -- |
| | | Serratia marcescens | ✓ |
| | | Viruses | |
| | | Herpes simplex virus | ✓ |
| | | HIV | ✓ |
| | | Influenza | ✓ |
| | | Epstein-Barr virus | ✓ |
| | | Cytomegalovirus | ✓ |
| | | Fungi | |
| | | Aspergillus spp | ✓ |
| | | Coccidioides immitis | ✓ |
| | | Histoplasma capsulatum | ✓ |
| | | Mucormycetes | -- |
| | | Rhizopus spp | ✓ |
| | | Cryptococcus neoformans | ✓ |
| | | Exserohilum rostratum | ✓ |
| | | Parasites | |
| | | Toenia solium | ✓ |
| | | Toxoplasma gondii | ✓ |
| | | Toenia solium | ✓ |
| | | Trypanosoma cruzi | ✓ |
| | | Plasmodium spp | ✓ |
| | | Acanthamoeba spp | -- |

Table 1: Mechanisms of infectious causes and triggers of stroke (Fugate et al. Lancet 2014)

Table 2: Major recognized pathogens implicated as infectious causes of ischemic and hemorrhagic stroke (Fugate et al. Lancet 2014)

Human Immunodeficiency Virus

Stroke was first reported early in the 1980s in patients with AIDS, most commonly associated with CNS opportunistic infections in the pre-combined antiretroviral treatment (cART) era (4). Effective cART therapy has transformed HIV infection into a chronic disease in resource-rich settings, with HIV-infected individuals living longer. Several observational cohort studies in the current era of highly effective cART have demonstrated higher rates of ischemic (5-8) and hemorrhagic (9-10) stroke in people living with HIV compared with HIV-uninfected controls, with an estimated 20 to 80% increase in risk after adjustment for established stroke risk factors. The burden of cerebrovascular disease in HIV infection is expected to rise as people living with HIV age (11). HIV infection can result in stroke via several mechanisms, including opportunistic

infection, vasculopathy, cardioembolism, and coagulopathy. HIV and associated infections contribute to chronic inflammation and HIV has been shown to cause direct vasculopathic effects including the development of fusiform aneurysmal cerebral vasculopathy (12). Pathological studies of both large and penetrating cerebral arteries of patients with HIV reveal thinning of the media, often accompanied by dilatation (13-15). Infarcts in HIV-positive patients are associated with arterial remodeling including accelerated atherosclerosis with severely stenotic vessels, and dilated, dolichoectatic vessels predisposing both to thrombotic and hemorrhagic strokes (16). Evidence has convincingly shown that cART results in a reduction of all-cause mortality in patients with HIV (17-18). Though, exposure to certain antiretroviral (ARV) treatments, including protease inhibitors which are associated with dyslipidemia, may increase the risk of stroke. In terms of primary and secondary prevention of stroke in HIV-infected patients, practitioners should consider modification of cART regimens to minimize adverse effects associated with stroke risk. Data suggests that the same measures for primary and secondary prevention of stroke in the general population exist in the HIV population, including monitoring and treatment of modifiable risk factors including hypertension and hyperlipidemia, though these measures to reduce the risk of stroke have been minimally studied in the HIV population.

Varicella Zoster Virus

Several viruses have been implicated in increasing the risk of ischemic and hemorrhagic stroke (Table 2). Varicella zoster virus (VZV) has been described to cause a CNS vasculopathy, particularly in immunosuppressed patients, either in the setting of acute infection (chickenpox) or in the context of reactivation. Shingles might be absent or precede the cerebrovascular symptoms by days to months (19). The pathogenesis of stroke following an episode of dermatomal zoster has been linked to direct viral invasion of cerebral arteries with VZV by extension along the intracranial branches of the trigeminal nerves resulting in an inflammatory process within the internal carotid artery or its branches ipsilateral to the branch (20-21). In many cases, VZV vasculopathy seems angiographically similar to other infectious and non-infectious vasculopathies, and can involve both large and small intracerebral vessels, which can make diagnosis challenging (22). Strokes related to VZV infection tend to affect the deep structures of the brain, including the basal ganglia and internal capsules, as well as the cerebral cortex supplied by the branches of the middle cerebral artery (20). Interestingly, recent evidence shows virological evidence of VZV in temporal arteries from patients with pathologically verified giant cell arteritis (GCA) (23). The effects of antiviral therapy and steroids on reduction of the long term risk of stroke after VZV infection are unknown.

Bacterial meningitis

Bacterial meningitis continues to result in substantial morbidity and mortality despite the availability of effective antimicrobial therapy and vaccines. Neurological complications including stroke can develop at any time during the course of bacterial meningitis. The subarachnoid inflammatory reaction from *Haemophilus influenzae*, *Streptococcus pneumoniae*, or *Neisseria meningitidis* may lead to ischemic strokes via several different mechanisms. Both small and large arteries may be occluded and thrombosis of the cortical veins and dural sinuses may occur. Direct extension of infection through the adventitia can lead to formation of brain aneurysms. Among 68 patients admitted to a neurologic intensive care unit with bacterial

meningitis, a reduced level of consciousness at the time of admission and a low white blood cell count in the cerebrospinal fluid (CSF) were found to be predictive factors for cerebral infarction (24). A number of other rare cerebrovascular complications have been described in isolated reports. These include hemorrhagic strokes, thrombotic infarction and subarachnoid hemorrhage (25-27). There is currently minimal data which exists showing the efficacy of adjunctive steroids in reducing stroke burden in the context of acute bacterial meningitis.

Tuberculous meningitis

Tuberculosis affects one third of the world's population and is one of the leading causes of morbidity and mortality. Tuberculous meningitis is the most severe manifestation of tuberculosis, with neurological involvement occurring more commonly in patients co-infected with HIV and in those with multidrug-resistant tuberculosis. Stroke is a common complication of tuberculous meningitis, and occurs in up to 30% of patients (28). Cerebral infarction in TBM is commonly related to a necrotizing arteritis of the vessels of the circle of Willis involving the basal meninges. Cerebral infarction in TBM is associated with a poor outcome, and most commonly found in the basal ganglia or subcortical white matter, in the distribution of the lenticulostriate arteries. Marked enhancement of the basal exudate is a risk factor for basal ganglia infarction. In a study evaluating the use of aspirin in prevention of stroke in patients with TBM, there was a nonstatistically significant reduction in the number of strokes and significant reduction in three month mortality (28). Prior studies have shown that corticosteroids may affect outcome from TBM by reducing hydrocephalus and preventing infarction, though prior studies have not shown that steroids results in a reduction of the occurrence of hemiplegia or paraplegia (29-30).

Infective endocarditis:

Infective endocarditis (IE) is an infection of the endocardial surface of the heart, which may include one or more heart valves, the mural endocardium, or a septal defect. Infarcts result from the embolization of endocardial vegetations with occlusion of an intracerebral artery. Dissemination of the emboli into cerebral or meningeal vessels can further lead to meningitis or intracerebral abscess formation (31-32). Neurological complications may be the presenting symptom in patients with infective endocarditis, and occurs in approximately 40% of IE patients (33-36). Mycotic aneurysm can develop in the cerebral or systemic circulation in the setting of IE, usually at points of vessel bifurcation. Early initiation of antibiotic therapy is essential to reduce the mortality and morbidity from embolic complications (37). Management of antithrombotic therapy (anticoagulant and antiplatelet agents) in patients with IE is challenging given the competing risks of embolism and intracerebral hemorrhage in this condition and limited evidence on the effects of therapy. Factors such as native versus prosthetic valve IE, size of the vegetation and its location on the mitral or aortic valve, virulence of the infective organism, size of the infarct(s), and presence of HT or mycotic aneurysms must be evaluated to assess the risks and benefits of initiation of antithrombotic therapy. Anticoagulant and antiplatelet therapy have not been shown to reduce the risk of embolism in IE. However, many patients with IE have indications for antithrombotic therapy, particularly patients with

mechanical prosthetic valves. In such patients, the potential risks and benefits of antithrombotic therapy must be carefully weighed.

Systemic infection risk:

Strokes has been associated with systemic infection and linked to the outcomes of chronic or indolent infections (38). In the Cardiovascular Health Study, a multicenter prospective cohort study of vascular risk factors in an elderly population, it was found that recent hospitalization for an infection including respiratory and urinary infections was associated with an increased risk of stroke (39). A recent study found that sepsis increased the risk of stroke as long as 365 days after an admission with sepsis (40). Proposed mechanisms for increased stroke risk in the context of systemic infection include increased platelet activation and aggregation, impaired endothelial function, infection provoked cardiac arrhythmias, and dehydration-induced thrombosis (41).

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