Infectious causes of stroke

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Most infectious pathogens have anecdotal evidence to support a link with stroke, but certain pathogens have more robust associations, in which causation is probable. Few dedicated prospective studies of stroke in the setting of infection have been done. The use of head imaging, a clinical standard of diagnostic care, to confirm stroke and stroke type is not universal. Data for stroke are scarce in locations where infections are probably most common, making it difficult to reach conclusions on how populations differ in terms of risk of infectious stroke. The treatment of infections and stroke, when concomitant, is based on almost no evidence and requires dedicated efforts to understand variations that might exist. We highlight the present knowledge and emphasise the need for stronger evidence to assist in the diagnosis, treatment, and secondary prevention of stroke in patients in whom an infectious cause for stroke is probable.

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Introduction

Stroke is a leading cause of death and disability worldwide.[1] Although established risk factors for stroke exist,[2,3] some infectious pathogens might confer additional risk either by increasing baseline tendency or having a direct causal role. Similarly to the prevention of traditional risk factors for stroke, several infections could be prevented and their disease incidence reduced. Because about 85% of strokes now occur in low-income and middle-income countries,[4] infectious strokes might be particularly important to consider in locations where few data are available. We review the range and influence of infectious organisms on stroke, with special consideration for regions where infectious diseases are most prevalent.

Systemic Infections

Ischaemic stroke has been associated with systemic infection and linked to the outcomes of chronic or indolent infections. Several findings suggest a possible association between systemic infection and stroke. The epidemiology of ischaemic stroke is insufficiently explained by the prevalence of traditional cerebrovascular risk factors.[5] A substantial proportion of patients who have had an ischaemic stroke lack these risk factors, and no apparent cause of stroke is identified in up to a third of cases. Additionally, stroke incidence rises during cold months, which leads to speculation that infections contribute to this seasonal fluctuation.[5]

Findings from case-control studies have consistently shown an association between systemic infection and stroke, with an odds ratio (OR) ranging from 2 to 14·5 for a preceding infection in individuals with stroke.[6–11] Because of heterogeneous definitions and outcomes, the findings from these studies are difficult to directly compare. An infection is generally defined as recent when occurring within the preceding 1–4 weeks; however, the specific organism or pathogen causing this infection is often not identified. One of the largest studies finding an association between acute infection and increased stroke risk included 19 063 people with a first-time stroke.[12] The risk of stroke was highest during the first 3 days after the diagnosis of respiratory tract infection (incidence ratio [IR] 3·19 [95% CI 2·81–3·62]) or urinary tract infection (2·72 [2·32–3·20]) and gradually decreased in subsequent weeks.[12] The database did not distinguish between ischaemic and haemorrhagic strokes.

Stimulation of the inflammatory response is thought to be the predominant mechanism linking ischaemic stroke with infection (table 1).[27–29] Inflammatory cascades promote atherosclerosis, plaque rupture, and thrombosis, leading to ischaemic stroke. High-sensitivity C-reactive protein in the blood might be an independent predictor of ischaemic stroke, but its precise association is unsettled.[30,31]

By contrast, very few published studies have assessed the association between systemic infection and intracranial haemorrhage. A systemic inflammatory response to infection can injure vascular endothelial cells and predispose patients to intracranial haemorrhage.[32] Findings from one case-control study (n=44 cases)[32] identified a borderline, statistically significant association between subarachnoid haemorrhage and infection within the preceding month, but the CIs of the association were wide (OR 4·5 [95% CI 1–21]). That study did not find an association between intraparenchymal haemorrhage and preceding infection; this lack of association with intraparenchymal haemorrhage was confirmed in a subsequent study of 56 patients with chronic bronchitis.[33] A larger, prospective study of 278 patients with intracranial haemorrhage also detected no association between intracranial haemorrhage and recent infection.[34]

Beyond acute infections, the concept of chronic infectious burden, a combined effect of chronically persistent pathogens or previous infections, or both, has been associated with atherosclerosis and stroke.[28] According to this theory, infections contribute to the overall inflammatory state of the atherosclerotic plaque.[28] One proposed mechanism describes direct pathogenic invasion of the vascular wall with proliferation of smooth muscle cells or an increase in cytokine production, or both. Alternatively, the infection might affect regions distant to the primary site of infection, with secondary injury causing damage to the arterial wall. Other mechanisms such as increased platelet aggregation and vasodilatory dysfunction have also been proposed.[28] The definition of infectious burden is not standardised, making synthesised conclusions difficult to reach on the basis of available studies. Furthermore, no consensus on

	Disorder	Study design	Definition of ischaemic stroke	Frequency of ischaemic stroke (%)*
Schut et al (2012)[14]	Bacterial meningitis	Case-control, prospective	Focal neurological signs with CT evidence	174/696 (25%)
Kastenbauer et al (2003)[15]	Pneumococcal meningitis	Case series, retrospective	Neurological examination and CT evidence	18/87 (21%)
Pfister et al (1992)[16]	Bacterial meningitis	Case series, prospective	Focal deficit or persistent coma and CT evidence	9/86 (10%)
Weisfelt et al (2006)[17]	Pneumococcal meningitis	Cohort, prospective	CT evidence	52/299 (17%)
Ozates et al (2000)[18]	Tuberculous meningitis	Case series, retrospective	CT evidence	39/289 (13%)
Murdoch et al (2009)[19]	Infective endocarditis	Cohort, prospective	Acute neurological deficit of vascular cause lasting >24 h	462/2727 (17%)
Cooper et al (2009)[20]	Left-sided infective endocarditis	Case series, prospective	New onset of a persistent focal neurological deficit	14/56 (25%)
Kang et al (2009)[21]	Herpes zoster	Cohort, retrospective	ICD9 430–438	439/7760 (6%)
Lin et al (2010)[22]	Herpes zoster ophthalmicus	Cohort, retrospective	ICD9 430–438	53/658 (8%)
Lee et al (2010)[23]	Hepatitis C infection	Cohort, prospective	ICD9 430–438	255 cerebrovascular deaths/382 011 person years (3% cumulative risk)
Rasmussen et al (2011)[24]	HIV infection	Cohort, retrospective	Diagnostic code from registries	38/5031 (1%)
Chow et al (2012)[25]	HIV infection	Case-control, retrospective	ICD code diagnosis	132/4308 (3%)
Nunes et al (2009)[26]	Chagas disease with dilated cardiomyopathy	Case series, prospective	New focal neurological deficit lasting >24 h	9/213 (4%)

*International classification of disease ninth revision codes (ICD9 430–438).[13]

Table 1: **Selected clinical studies showing the frequency of ischaemic stroke in the setting of known infectious illness**

how to measure infectious burden, including which organisms should be considered and confirmed, exists. The most commonly studied organisms linked to heightened stroke risk include *Helicobacter pylori, Chlamydia pneumoniae, Mycoplasma pneumoniae, Haemophilus influenzae*, Epstein-Barr virus, herpes simplex virus (HSV)-1 and HSV-2, and cytomegalovirus (table 2). Speculation surrounds whether an association exists between oral cavity infections (periodontitis and gingivitis) and atherosclerotic vascular disease.[35,36] Because information is derived mainly from observational studies, causality is unclear.[37]

Associations between infectious burden and vascular disease might show the burden of other confounding underlying risk factors that directly cause atherosclerosis. For example, people with several medical comorbidities or who smoke cigarettes might also have a high prevalence of common infections.[30]

Infective endocarditis

Infective endocarditis is a notable cause of cardioembolic stroke. Stroke occurred in 17% of 2781 adult inpatients with infective endocarditis enrolled in a prospective cohort study done in 25 countries.[19] The risk of stroke was highest at presentation of infective endocarditis and declined within 1–2 weeks after antibiotics were initiated. In another study[38] of 1437 patients, the incidence of stroke fell from 4·8 per 1000 patient-days in the first week of antibiotic treatment to 1·7 per 1000 patient-days in the second week.[38] Risk factors for stroke in infective endocarditis included delayed initiation of antibiotics, infection with *Staphylococcus aureus*, large valvular vegetations, and immunosuppression.[38]

Embolism to the brain in a patient with infective endocarditis could be clinically silent. In one prospective study of 56 patients with left-sided endocarditis, embolisation to the brain was detected on MRI scan in 80% of cases and was subclinical in 48%.[20] Asymptomatic embolism was less frequent but still substantial in a large prospective series of 130 patients of whom only 12% had neurological symptoms, but 52% had ischaemic lesions and 57% had microhaemorrhages on MRI scans within 7 days of admission.[39]

S aureus, β-haemolytic streptococci, and *Streptococcus viridans* are the most frequently identified pathogens in infective endocarditis complicated by intracranial haemorrhage.[40] Degradation of the arterial wall by bacteria or septic embolisation causes abnormal dilatations or mycotic aneurysms. These aneurysms can be numerous and occur at distal portions of the middle cerebral artery, and their rupture is associated with a high mortality rate.[41]

Primary intracranial infections

Bacteria

Bacterial meningitis

The prevalence of stroke complicating meningitis depends on the bacterium and definition of stroke. In a prospective, case-control study in the Netherlands, brain