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Inflammation, Autoimmunity, Infection, and Stroke: Epidemiology and Lessons from Therapeutic Intervention

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Inflammation, a complex response to danger signals that is fundamental to host survival, has been implicated in the pathogenesis of many human diseases, including stroke.[1] In this review, we discuss the impact of inflammation, including in the context of autoimmune conditions and infectious diseases, on ischemic stroke risk and outcomes (Figure). We complement a critical evaluation of epidemiological evidence with results of intervention studies.

Inflammation and Inflammatory Markers

Inflammation is a coordinated response to both extrinsic and intrinsic danger signals associated with innate and adaptive immunity.[2] Foreign molecular complexes common to many infectious pathogens, termed pathogen-associated molecular patterns, are recognized by immune cell pattern recognition receptors, which, in turn, initiate innate and adaptive immune responses directed at neutralizing the threat. Similarly, host-derived danger-associated molecular patterns released from host cells during injury or stress engage pattern recognition receptors triggering immune responses. Immune cell activation leads to cascading effects on local and distant systems through the release of chemokines and

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cytokines. Co-activation of immune regulatory mechanisms leads to eventual resolution of inflammation. The molecular mechanisms that trigger, sustain, and resolve inflammation are multiple and complex, and are outside this scope of this review. Broadly, however, aberrations of these immune-regulatory processes can lead to under-active, over-active, non-resolving, or otherwise maladaptive inflammatory responses that can contribute to disease risk, pathology and tissue injury.

Inflammatory biomarkers, stroke risk, and outcomes

Inflammatory biomarkers include the cytokines, chemokines, and acute phase reactants that govern the inflammatory response. Elevations in inflammatory mediators interleukin-6 (IL-6), c-reactive protein (CRP), and lipoprotein-associated phospholipase A2 (Lp-PLA2) have been associated with increased stroke risk.[3] An additional biomarker of increasing interest is soluble lectinlike oxidized low-density lipoprotein receptor-1, which is an inflammation-induced lipid receptor that contributes to atherogenesis and has been associated with stroke risk.[4, 5] Elevated CRP was also associated with stroke recurrence[6] in addition to recurrent vascular events, vascular death, and non-vascular death.[7–10] IL-6 and Lp-PLA2 have similarly been linked to stroke recurrence, post-stroke myocardial infarction, and death.[8, 11–16] The bulk of evidence supports an association between elevated inflammatory biomarkers and an increased risk of stroke, recurrent stroke, and post-stroke vascular events and mortality.

In addition to stroke recurrence, sources of post-stroke disability include physical disability, cognitive impairment, depression, and fatigue. Inflammatory biomarkers have been extensively studied as putative predictors of functional outcomes after ischemic stroke.[17] Although the data are heterogeneous, several studies found elevated CRP to be independently associated with poor clinical outcomes after stroke.[17, 18] IL-6, an upstream inflammatory cytokine, has more robustly been associated with poor functional outcomes in large meta-analysis.[19] With respect to cognitive outcomes, limited data suggest that CRP,[20] interleukin-12,[21] and erythrocyte sedimentation rate,[22] but not IL-6,[20, 21] are associated with post-stroke cognitive impairment. Data regarding post-stroke depression are conflicting,[23] with no evidence of an association between CRP levels and post-stroke depression in a recent multi-center prospective study.[24] Evidence regarding post-stroke fatigue is similarly limited, with most studies including less than 50 subjects.[25] CRP was also not consistently associated with fatigue across studies.[26] In summary, inflammatory biomarkers at the time of stroke are fairly consistently associated with functional outcomes, but data regarding post-stroke cognitive impairment, depression, and fatigue are not definitive.

Insights from therapeutic trials

A causal association between inflammatory biomarkers and stroke risk can be inferred from clinical trials of immunomodulatory therapies. The Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) seminally demonstrated that rosuvastatin for individuals with elevated hsCRP levels and with normal low-density lipoprotein C (LDL-C) levels reduced cardiovascular risk, including for the secondary outcome of stroke.[27, 28] Rosuvastatin reduced stroke risk in subjects who either achieved LDL-C levels of < 70 mg/dL or hsCRP levels of <2 mg/L. Importantly, achieved

LDL-C and hsCRP levels had poor correlation, suggesting that risk reductions could also be attributed to anti-inflammatory effects of rosuvastatin alone. This hypothesis was then specifically tested in the Canakinumab Antiinflammatory Thrombosis Outcome Study, which randomized patients with a history of myocardial infarction and elevated hsCRP level to canakinumab, a monoclonal antibody against interleukin-1beta, or placebo.[29] Canakinumab reduced HsCRP levels in a dose-dependent fashion, without impact on LDL-C levels. There was a dose-dependent reduction in the primary cardiovascular disease (CVD) outcome, and stroke risk was nominally reduced in patients on the highest dose. In contrast, a related trial of methotrexate did not demonstrate reductions in inflammatory markers or CVD risk.[30] Taken together, these data suggest that reduction of hsCRP, whether with statin therapy or canakinumab, results in a reduction of CVD risk, including stroke.

Trials of immunomodulatory therapy for the prevention of post-stroke unfavorable outcomes are few. The Japan Statin Treatment Against Recurrent Stroke trial randomized patients with prior stroke to pravastatin or placebo, and a secondary analysis evaluated whether changes in hsCRP were associated with recurrent event risk.[31] Like in JUPITER, achieved LDL and achieved hsCRP levels did not correlate. Higher hsCRP levels during treatment were associated with a greater risk of recurrent stroke and vascular events. With regards to post-stroke functional outcomes, in an exploratory analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial, high dose atorvastatin was non-significantly associated with better functional outcomes compared to placebo ($p=0.065$).[32] In a meta-analysis, statin therapy at the time of stroke was associated with less post-stroke disability.[33] Last, two immunomodulatory multiple sclerosis therapies have been trialed in ischemic stroke. Natalizumab, a monoclonal antibody that reduces leukocyte infiltration, did not lower final infarct volumes but marginally improved functional outcomes.[34] Fingolimod, an immunomodulator that reduces circulating lymphocytes, limited infarct volume and hemorrhagic transformation and improved functional outcomes when added to alteplase.[35]

Other stroke outcomes have been less studied. In the natalizumab trial mentioned above,[34] exploratory analyses found non-significantly improved cognitive and mood outcomes with among those randomized to natalizumab. In the absence of trials of anti-inflammatory therapies for post-stroke cognitive impairment, depression, and fatigue, pharmacoepidemiology studies provide insights. A registry analysis found that anti-inflammatory treatment at the time of stroke was associated with a lower risk of depression within the first year.[36] While data are conflicting,[37] a prospective cohort study found that statins reduced the risk of post-stroke depression.[38] Mechanistically, admission IL-6 levels have been associated with post-stroke depression at 1 year among statin non-users but not among statin-users.[39] These data suggest that statins may ameliorate post-stroke inflammatory drivers of depression. Taken together, there is circumstantial evidence of a therapeutic effect of anti-inflammatory treatments on post-stroke outcomes. Trials that strategically target inflammation are needed.

Autoimmune disorders and ischemic stroke

Autoimmune disorders are frequently associated with stroke risk and provide insights into the impact of inflammation on cerebrovascular disease (Figure). Here, we focus on

autoimmune disorders characterized by chronic systemic inflammation (Table 1). Cerebral vasculitides were reviewed elsewhere.[40]

Rheumatoid arthritis

Rheumatoid arthritis (RA) is associated with an increased risk of CVD and has been included alongside conventional risk factors in a CVD risk score.[41] Data specific to stroke are less abundant but consistent. A meta-analysis found that patients with RA had 1.6 times the odds of stroke as the general population, including when accounting for corticosteroid use.[42–44] Although patients with RA have more vascular risk factors, this alone does not explain the increased risk of CVD since both conventional risk factors and markers of RA disease activity and severity, including elevated inflammatory markers, are associated with CVD risk.[45–49] In administrative claims analyses, RA was associated an increased risk of recurrent stroke[50] but not other stroke outcomes.[51] Several pharmacoepidemiological studies, including a meta-analysis, provide mixed evidence that disease-modifying immunomodulatory therapies reduced CVD and stroke risk.[52–54] In summary, RA is consistently associated with an increased stroke risk, and that risk can in part be attributed to inflammation, but whether targeting this inflammation reduces stroke risk remains unclear.

Systemic lupus erythematosus

In a recent meta-analysis, systemic lupus erythematosus (SLE) was associated with a two-fold increased odds of stroke compared to the general population.[42] However, a subsequent large cohort study did not find an association.[44] In an additional subsequent cohort study, SLE was not associated with stroke after accounting for steroid therapy as a confounder.[55] Apart from inflammation, stroke mechanisms in SLE include cerebral arteritis, anti-phospholipid syndrome, and cardioembolism due to non-infectious endocarditis. Nephritis and related hypertension may also directly contribute to atherosclerosis and myocardial infarction risk.[56, 57] Lastly, active steroid use is associated with CVD in patients with SLE.[58] Therefore, there is insufficient evidence that SLE increases stroke risk through inflammation alone. Consistent with this notion, there is comparatively little data regarding disease modifying drugs and CVD risk in SLE.

Inflammatory bowel disease

Inflammatory bowel disease is associated with a modestly increased risk of stroke, with a meta-analysis reporting a hazard ratio of 1.3.[59] Most studies reported an increased risk of stroke for both ulcerative colitis and Crohn’s disease, with the exception of two studies that found an association only for ulcerative colitis.[60, 61] Several studies found the risk of stroke to be increased during times of greater disease activity.[60, 62] Although the increased risk could also be attributable to treatment or detection bias, the evidence generally indicate that stroke is an inflammatory complication of these disorders.

Psoriasis

Psoriasis, with or without arthritis, is also associated with an increased stroke risk, with stroke risk paralleling disease severity.[42, 63, 64] Disease duration was associated with vascular inflammation, assessed with ^{18}F-fludeoxyglucose positron emission tomography,

and ischemic stroke.[65] A meta-analysis of observational studies found that systematic anti-inflammatory therapies were associated with a significantly decreased CVD risk compared to no systemic therapy or topical therapy.[52] TNFα inhibition was associated with nearly an 50% reduction in stroke and transient ischemic attack, compared to methotrexate.[66] Similarly, TNFα inhibition was associated with a lower CVD risk than phototherapy, despite phototherapy being used in milder cases.[67] These data, in concert with the correspondence between psoriasis severity and duration and stroke, support a causal relationship between inflammation and stroke in this condition.

Other systemic inflammatory diseases

Other conditions preliminarily associated with stroke include ankylosing spondylitis,[68] polymyalgia rheumatica,[69] polymyositis, and dermatomyositis.[70] In polymyalgia, cumulative exposure to glucocorticoids was associated with a tendency towards a decreased stroke and CVD risk.[71] Because treatment with high dose steroids is typical in patients with more active disease, this finding raises the possibility that the anti-inflammatory effect of glucocorticoids mitigated the increased stroke and CVD risk.

To summarize, the autoimmune conditions reviewed here are associated with an increased stroke risk, with evidence of a dose-response relationship with disease duration and severity. Furthermore, targeting inflammation in some of these conditions reduces or mitigates stroke risk. These data provide clinical complement findings of inflammatory biomarker studies.

Chronic Infection and Ischemic Stroke

Inflammation is also seen in infectious diseases. Here we focus on select infectious conditions that may impact stroke risk and outcomes through inflammation (Table 2). Infectious diseases that cause stroke through other mechanisms were comprehensively reviewed elsewhere[72] and are not discussed.

Infectious Burden, Systemic Infections, and Stroke

Chronic infectious burden, the cumulative exposure to persistent or previous infections,[73] may be associated with an increased stroke risk (Figure). Underlying mechanisms may include endothelial dysfunction and vascular inflammation promoting atherosclerosis,[73, 74] and vascular injury from direct pathogenic invasion of the vessel wall.[72–74] The chronic infectious burden construct includes *Chlamydia pneumoniae, Mycoplasma Pneumoniae, Helicobacter pylori, Hemophilus influenza, Herpes simplex* 1 and 2 (HSV), *Cytomegalovirus* (CMV), and *Epstein Barr* virus (EBV). The Northern Manhattan Study found an 1.4-fold increased risk of stroke among patients with high chronic infectious burden, defined by seropositivity.[75] However, others have not replicated this finding, for example when adjusting for socioeconomic counfounders.[76] Further studies are needed to understand whether chronic infectious burden confers an independently increased stroke risk.

Bacterial infections

Several chronic bacterial infections have been variably associated with stroke risk. Periodontitis, a polymicrobial destructive disease of the gums and supportive tissues, may increase stroke risk through systemic inflammation.[77] For example, periodontal disease was associated with an increased risk of ischemic stroke in the Atherosclerosis Risk in Communities cohort.[78] Periodontitis was independently associated with an increased stroke risk in a meta-analysis as well.[79] Chronic osteomyelitis, another indolent infectious condition, was associated with an increased stroke risk in an administrative claims analysis.[80] Finally, peptic ulcer, a common disease caused by *Helicobacter pylori*, was not associated with stroke in a recent, updated meta-analysis.[81]

Viral infections

Several chronic viral infections have also been implicated. CMV, a prevalent DNA herpesvirus, was observed in atherosclerotic plaque, raising the possibility that it contributes to atherosclerosis.[82] CMV was not associated with stroke in the Framingham Heart Study,[83] the Northern Manhattan Study,[75] or in a meta-analysis.[84] However, the Vascular effects of Infection in Pediatric Stroke study found that serological evidence of acute herpesvirus infections (a combination of HSV, CMV, EBV, and varicella zoster virus [VZV]) was associated with a two-fold odds of stroke.[85] The lack of competing conventional risk factors may make infectious etiologies more relevant in children. In adults, hepatitis C virus (HCV) was associated with a two-fold increased risk of cerebrovascular death in a large cohort study, and a dose-response relationship with HCV RNA levels was seen.[86] Furthermore, anti-viral treatment has been associated with a decreased ischemic stroke risk.[87]

Neurovascular Infections

Multiple infections lead to cerebral arterial inflammation through direct arterial wall invasion or immune complex deposition (Figure).[88]

Strokes can occur from tuberculosis meningitis, a progressive, necrotizing meningoencephalitis.[89] It causes an exudative encasement and infiltration of vessels, leading to endarteritis.[89] This, combined with mechanical stress from hydrocephalus,[90] leads to stroke predominantly in the deep structures. Strokes occur in approximately 6% of cases of pulmonary tuberculosis and up to 20% of patients with tuberculous meningitis.[91, 92] Stroke risk is also heightened among patients with pulmonary tuberculosis alone, compared to uninfected controls.[91]

Neurological involvement occurs in 10% of cases of untreated syphilis.[93] Approximately 10% of patients with neurosyphilis, and 3% with any syphilis, develop stroke.[93, 94] Patients with stroke are often young and with fewer conventional stroke risk factors, and may experience a prodrome of headache, malaise, and behavioral changes.[95] The mechanism of stroke in syphilis is thought to be due to inflammation of the arterial wall secondary to an obliterative endarteritis of the medium to large arteries. Lyme disease, caused by *borrelia burgdorferi*, is another disease with protean cerebral manifestations including stroke.[96] Stroke is thought to be due to an inflammatory vasculitic process of the cerebral vasculature.[97]

In a recent meta-analysis, HIV was associated with 1.8 times higher stroke risk compared to non-infected individuals.[98] Lower CD4 counts and unsuppressed viral load were risk factors. HIV affects the central nervous system days after systemic infection and produces an inflammatory cascade within the cerebrospinal fluid and the brain parenchyma.[99] On autopsy, arteries from HIV positive patients had more inflammation than arteries from HIV negative controls, though the association was attenuated after adjusting for possible confounders.[100] Individuals with HIV have accelerated atherosclerosis, exemplified by higher carotid intima-media thickness and coronary artery calcium progression.[101] Individuals with HIV also have evidence of arterial remodeling – leading to atherosclerosis and dolichoectasia – which may be a consequence of arterial inflammation.[102]

Following VZV (chickenpox) infection, VZV becomes latent in ganglionic neurons throughout the neuroaxis, and reactivation causes herpes zoster (shingles).[103] VZV can also directly infect large and small cerebral arteries to cause a vasculopathy, resulting in both ischemic and hemorrhagic stroke.[103, 104] In a meta-analysis, zoster was associated with a 1.5-fold increased stroke risk for four weeks after zoster.[105] The risk of stroke was up to 4.5 times higher in the first 12 months after zoster ophthalmicus.[106] The observation that antiviral treatment may mitigate stroke risk[105] increases confidence in the causality of VZV's association with stroke. Although the strength of associations and exact mechanisms vary, epidemiological data support the notion that several microbial infections are independent stroke risk factors, often acting through chronic inflammation.

Post-infectious stroke and post-stroke infection

There is a short-term increase in stroke risk after multiple acute infections. In a large, self-controlled case series analysis[107] and in the Cardiovascular Health Study,[108] short-term stroke risk markedly increased after respiratory and urinary infections. Influenza-like illnesses and sepsis also appear to increase short-term stroke risk.[109, 110] The inflammatory response to the infection is thought to contribute to accelerated atherosclerosis, plaque rupture, and thrombosis.[72, 111] Conversely, due in part to post-stroke immunosuppression,[2] the rate of infection after stroke is as high as 30%.[112] Infections, often pneumonia and urinary infections, are associated with poor outcomes and mortality.[113, 114] However, a meta-analysis found that randomization to prophylactic antibiotics reduced infection risk without improving outcomes.[115] Therefore, whether infection silently precedes stroke, is an epiphenomenon, or causally linked to outcomes remains unclear.

Conclusions

A rich body of literature demonstrates that inflammation is associated with increased stroke risk and may be an important determinant of outcomes. Data from pharmacological interventions and the study of autoimmune and infectious diseases provide additional support of a causal relationship between inflammation and increased stroke risk and severity. Currently, there is insufficient evidence to support the use of immunomodulatory therapies specifically to reduce stroke risk or improve outcomes. However, trials of newer immunomodulatory therapies, such as fingolimod and targeted inflammatory cytokine-neutralizing antibodies, combined with improved patient selection, may yield effective

interventions to reduce the burden of stroke risk and improve stroke outcomes among the general population and in individuals with autoimmune and infectious diseases.

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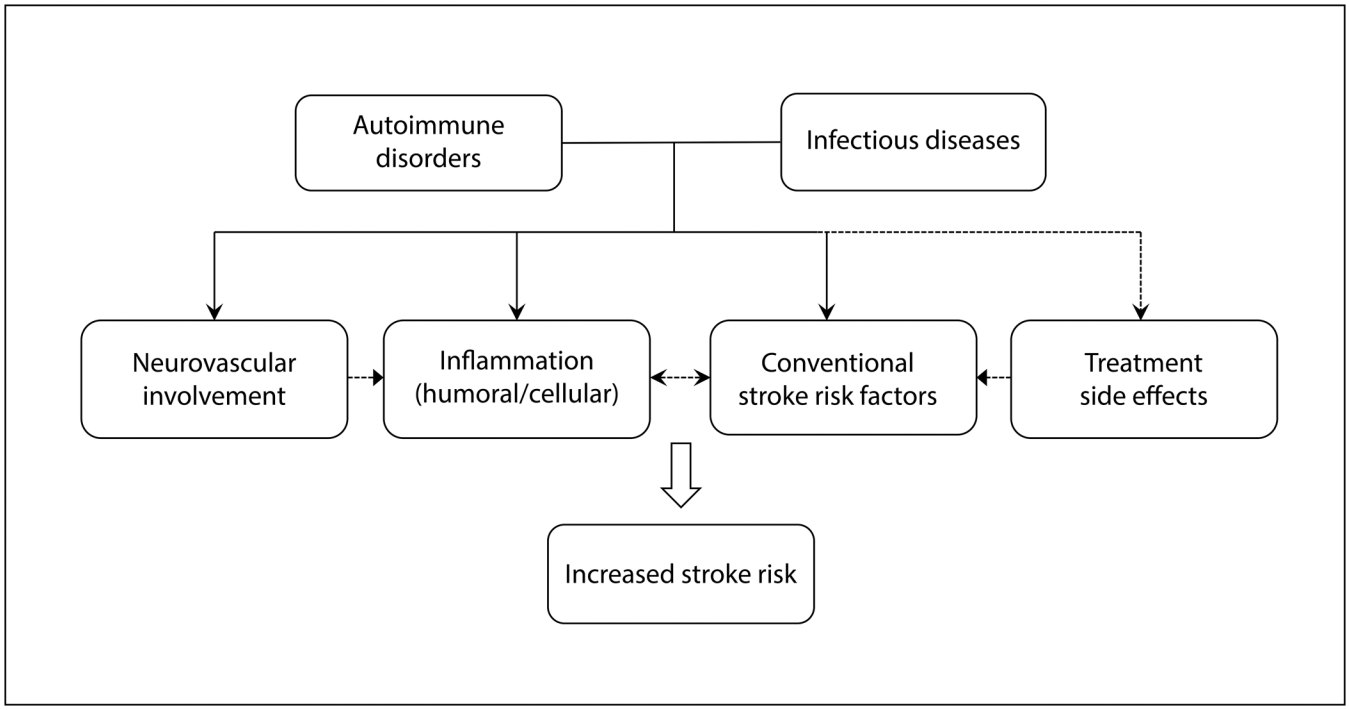

Figure. Putative mechanisms of increased ischemic stroke risk in autoimmune disorders and infectious diseases

Autoimmune disorders and infectious diseases share overlapping mechanisms that may contribute to an increased risk of ischemic stroke. Apart from cerebral vasculitis, autoimmune disorders contribute to ischemic stroke risk through multiple mechanisms. Increased systemic inflammation may itself increase stroke risk and magnify the effect of conventional stroke risk factors, which are common comorbidities in individuals with autoimmune disorders such as rheumatoid arthritis. Treatment of autoimmune disorders often involves the use of glucocorticoids, which may worsen control of conventional stroke risk factors such as diabetes and hypertension. Similarly, some infectious diseases contribute to ischemic stroke through infectious cerebral vasculitis. Infectious diseases, especially chronic diseases, also contribute to systemic inflammation and are associated with a higher burden of conventional stroke risk factors, such as atherosclerosis in the case of human immunodeficiency virus.

Table 1.

Select autoimmune conditions and data* regarding associations with ischemic stroke risk

Autoimmune condition	Association with ischemic stroke†	Dose-dependence‡	Reduction with anti-inflammatories§
Rheumatoid arthritis	+++	++	+
Systemic lupus erythematous	+	−	−
Inflammatory bowel disease	++	+	−
Psoriasis	++	++	+
Ankylosing spondylitis	+	−	−
Polymyalgia rheumatica	+	−	+
Inflammatory myositis	+	−	−

*The strength of associations was judged based on the number, quality, and consistency of studies for each metric. Where meta-analyses were available, the totality of evidence was considered. The following categories of strength of evidence were used: +++, Compelling evidence; ++, Modest evidence; +, Limited evidence; −, No evidence.

†Association with ischemic stroke was evaluated based on studies investigating the epidemiological association between individual conditions and stroke risk.

‡Dose-dependence was inferred from studies that investigated the association between severity or duration of each condition and ischemic stroke risk.

§Results of pharmacoepidemiological studies investigating the association between treatment and stroke risk were evaluated.

See text for synthesis, summaries and results of individual studies, and references.

Table 2.

Select chronic infections and data* regarding associations with ischemic stroke risk

Infection	Association with ischemic stroke	Dose-dependence	Reduction with infection control
Tuberculosis	+++	++	++
Syphilis	++	−	++
Lyme disease	++	−	+
Human immunodeficiency virus	++	++	++
Varicella zoster virus	+++	−	+
Cytomegalovirus	−	−	−
Hepatitis C virus	+	+	+
Helicobacter pylori	−	−	−
Chronic osteomyelitis	+	−	−
Periodontal Disease	++	+	+

*Please refer to Table 1 footnote for details.