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New Directions in Infection-Associated Ischemic Stroke

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The relationship between infections and stroke has not been fully characterized, probably delaying the development of specific treatments. This narrative review addresses mechanisms of stroke linked to infections, including hypercoagulability, endothelial dysfunction, vasculitis, and impaired thrombolysis. SARS-CoV-2, the virus that causes COVID-19, may promote the development of stroke, which may represent its most severe neurological complication. The development of specific therapies for infection-associated stroke remains a profound challenge. Perhaps the most important remaining issue is the distinction between infections that trigger a stroke versus infections that are truly incidental. This distinction likely requires the establishment of appropriate biomarkers, candidates of which are elevated levels of fibrin D-dimer and anticardiolipin/antiphospholipid antibodies. These candidate biomarkers might have potential use in identifying pathogenic infections preceding stroke, which is a precursor to establishing specific therapies for this syndrome.

Keywords stroke; thrombosis; infections; fibrin D-dimer; anticardiolipin/antiphospholipid antibodies.

Infections have long been suggested as precipitating factors for stroke.[1-3] The lack of appropriate experimental models has made it difficult to determine whether a specific infection is directly causal for the development of stroke. This review addresses the pathogenesis of stroke preceded by infections, and the therapeutic implications of infection-related stroke.

HYPERCOAGULABILITY AND THROMBOSIS

The immune system activation and inflammation occur after infection to eliminate infectious agents from the host. However, overactivation of these pathways can produce pathophysiological thrombotic and thromboembolic events.[4] Various exogenous pathogens (i.e., infectious agents)[5,6] can directly interact with endothelial cells, platelets, and leukocytes. Endogenous triggers (i.e., damage-associated molecular pattern molecules)[7] and host immune responses can directly or indirectly also lead to endothelial dysfunction, alterations in the vessel wall integrity and vasomotor tone, activation of leukocytes and platelets, and decreases in antithrombotic mechanisms (e.g., fibrinolysis and inhibition of thrombin generation).[8] Adhesion molecules such as P-selectin, E-selectin, vascular cell adhesion molecule-1, and intracellular adhesion molecule-1 can be upregulated in endothelial cells by bacterial products, viruses, and proinflammatory cytokines, resulting in an interplay of endothelial cells with platelets, neutrophils, and monocytes.[9] Also, activated vascular endothelial cells express and synthesize molecules that are vital to intravascular coagulation, including von Willebrand factor, tissue factor, and plasminogen activator inhibitor type 1 (PAI-1).[10]

Thrombin and other related coagulation enzymes, and thus the development of intravascular coagulation, are also controlled by several complicated direct and indirect mechanisms.

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These include reversible and irreversible protease inhibitors, enzymes, receptors, and proteins such as tissue-factor pathway inhibitor (TFPI), antithrombin, thrombomodulin (i.e., an endothelial integral membrane protein critical for the activation of circulating protein C),[11] and activated protein C (APC). Plasmin and other fibrinolytic mechanisms help to remove intravascular clots (thrombi). Some infectious agents can directly or indirectly damage the endothelium, leading to its activation/dysfunction, increased vascular permeability, and even activation of the contact complex (prekallikrein, coagulation factors XII and XI, and the proteinase inhibitor kininogen 1), causing both thrombin generation and inflammation. Numerous effects have been observed in certain infections, sepsis, and stroke patients with antecedent infection/inflammation, including decreased activity of TFPI released by endothelial cells,[12,13] increased release of PAI-1 from activated endothelia and platelets[9] (suppressing intrinsic thrombolysis), impaired protein C system (via the depletion of the decreased hepatic expression or gamma carboxylation of protein C and protein S), reduced thrombomodulin and endothelial protein C receptors (EPCRs) in endothelial cells,[14] and a decreased level of antithrombin.[15] Thrombi can thus form when there is a local or systemic procoagulant state during infection due to the presence of a pathological imbalance between hemostatic/procoagulant and antithrombotic/anticoagulant mechanisms.[16]

The regulation of hemostasis and thrombosis varies across different organs. The brain's unique cellular milieu has specific consequences for the regulation of these factors.[17] This has led to the concept of brain-specific regulation of thrombosis and hemostasis, a likely contributor to the vulnerability of the brain to the thrombotic consequences of infections.[17] One of the most-prominent elements of brain-specific regulation of thrombosis and hemostasis relates to expression of thrombomodulin. Early studies reported a surprising absence of thrombomodulin from brain capillaries.[18] Later studies demonstrated particularly low abundance of thrombomodulin in regions where small deep infarcts are most common.[19] Astrocyte-dependent transforming growth factor-beta-mediated transcriptional regulation resulted in restricted expression of brain capillary thrombomodulin.[20] Note that the activation of protein C is demonstrable during carotid artery clamping, suggesting the presence of at least some functioning brain thrombomodulin.[21] Features similar to thrombomodulin were demonstrated for brain capillary fibrinolysis, with restricted expression of the critical endogenous fibrinolytic molecule tissue plasminogen activator and with relative overabundance of PAI-1.[22,23]

Elevated levels of anticardiolipin antibodies (aCL) as a thrombogenic factor have been reported in patients with stroke preceded by infection.[24,25] Antiphospholipid antibodies (aPL) including anti-β_2-glycoprotein I antibodies (anti-β_2-GPIs) as well as lupus anticoagulant (LA) may be induced by various infections from viral, bacterial, parasitic, and fungal sources. Among them, antibodies against domain I of β_2-GPIs were found to be associated with thrombosis.[26] However, infection-induced aPL can be transient and is not necessarily associated with thrombosis. A systematic review[27] of case reports of antiphospholipid syndrome (APS) following infection found that most (68.3%) of the 293 cases developed APS or transient aPL with thromboembolic events, but the others did not experience such events. Of various clinical presentation, stroke or transient ischemic attack (TIA) was observed in about 23% of cases. aCL (91.8%) were most frequently reported in cases with APS or thromboembolic events, whereas positivity for LA (92.3%) was more commonly observed in patients without clinical events.

The mechanism of aPL production in infections includes antigen-dependent processes such as molecular mimicry of infectious agents and antigen-independent mechanisms such as impairment of immune tolerance caused by inflammation.[28] The pathogenesis of aPL-mediated coagulopathy was proposed as the activation of endothelial cells, complement, platelets, neutrophils, and monocytes by β_2-GPI–anti-β_2-GPI complexes, resulting in both coagulation and inflammation.[29] The association between aPL and thromboembolic events is now better understood with the discovery that the EPCR as a primary target of aPL participates in anticoagulation via the activation of protein C.[30] Thrombosis was generated in mouse models by aPL recognition of the endosomal lysobiphosphatidic acid–EPCR complex in various cell types and the subsequent cascade of coagulation and inflammation.[31] Moreover, a strong inverse correlation was found between the IgG aCL titer and the level of circulating APC (r=-0.55, p< 0.001) in patients with acute ischemic stroke preceded by infection.[13] In addition, elevations of fibrin D-dimer (indicating fibrin generation and lysis) and inflammatory marker C-reactive protein (CRP) have been found in patients with brain infarction preceded by infection.[25,32] Thus, the combined presence of coagulation activation and elevated aCL can provide important clues to the diagnosis of infection-associated stroke.

VASCULITIS AND DIRECT VASCULAR INJURY BY INFECTIONS

Vasculitis attributed to direct and indirect injury to endothelial cells from infections and the host immune-inflammatory response is probably one of the important etiologies in infection-related stroke. Suspected pathophysiological mech-

anisms include direct cellular injuries from microbial antigens, proinflammatory cytokines, and recruitment of immune cells resulting in endothelial damage and dysfunction/microthrombosis.[9,33] Animal models of vasculitis induced by bacterial (e.g., *Chlamydia pneumoniae*) and herpesvirus infections support the association of infection with vasculitis.[34]

Multiple infectious agents can infect the arterial wall during central nervous system (CNS) infection to directly induce stroke. The size, location, and number of involved cerebral blood vessels by a specific pathogen are expected to determine the infarct pattern and stroke subtype. Neurosyphilis results from CNS infection by *Treponema pallidum*; meningovascular syphilis causes stroke and meningitis that occur between the early and late forms of the disease.[35] Endothelial inflammation by syphilis eventually results in stroke by small-vessel occlusion.[36] Systemic tuberculosis, a chronic mycobacterial granulomatous infection, is one of the most prevalent infectious diseases worldwide, and is associated with an increased risk of ischemic stroke. A more direct mechanism is at play in tuberculous meningitis, where the vessels at the base and cortical branches of the brain are at particular risk of vasculitis and resultant strokes.[37,38] Tuberculous meningitis or neurosyphilis can appear as opportunistic infections in immunocompromised patients, such as those with human immunodeficiency virus (HIV). Infective endocarditis is characterized by infection of the endocardial surface, commonly involving the cardiac valves, by various organisms.[39] Ischemic lesions are typically multiple and bilateral, consistent with cardioembolic stroke.[40] Infective endocarditis often leads to septic emboli and bacterial seeding of the arterial wall, which can result in inflammation and subsequent aneurysmal formation (mycotic aneurysm).[41]

Varicella-zoster virus (VZV) can infect cerebral arteries by spreading in the vessel wall, thereby causing direct cerebral arteriopathy and ischemic stroke, intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (Fig. 1). Nagel and colleagues[42,43] described the presence of VZV DNA in cerebral arteries from the autopsied brain of a male who died of suspected CNS vasculitis. Those authors also reported that VZV can affect both small and large vessels. Another study by Gilden et al.[44] showed the detection of VZV antigen in the temporal arteries of 74% of patients with biopsy-proven giant-cell arteritis (GCA). However, this observation has not yet replicated by any other group. VZV spreading to extracerebral arteries remains inconclusive as a culprit of GCA.

Herpes simplex virus (HSV) is the cause of acute viral encephalitis in 50%–70% of cases in which a viral etiology can be identified.[45] HSV can induce infectious cerebral vasculopathies (involving the small or large vessels, or both) and subsequent ischemic and hemorrhagic strokes as CNS complications.[46] A systematic review of published cases indicated that HSV was associated with specific stroke manifestations, with HSV type 1 related to ICH due to vascular disruption by a necrotizing process, and HSV type 2 related to multifocal cerebral infarction attributed to large-vessel vasculitis.[47] Cytomegalovirus (CMV), which also a member of the herpesvirus family, activates the immune system in atherosclerotic plaques and causes vasculopathy similar to VZV.[48] Association of CMV infection with cardiovascular disease and stroke were also demonstrated in a meta-analysis.[49] In addition, HSV, hepatitis C virus, *Chlamydia pneumoniae*, *Helicobacter pylori*, *Porphyromonas gingivalis*, and *Aggregatibacter actinomycetemcomitans* have been found in atherosclerotic carotid and coronary vessels, and may contribute to the progression of atherosclerosis lesions.[50-54] These observations suggest that certain pathogens such as *Chlamydia pneumoniae* are associated with an increased risk of stroke due to large-artery atherosclerosis.[55]

HIV increases the risk of stroke by direct infection and indirectly by increasing the effects of traditional vascular risk factors for stroke.[56,57] HIV-related strokes may manifest as large-artery atherosclerosis, cardioembolism, small-vessel disease, coagulopathy, and HIV-associated vasculopathy.[58] A characteristic HIV vasculopathy involves arterial remodeling, with inward remodeling causing vessel stenosis and atherosclerosis, and outward remodeling leading to thinning of

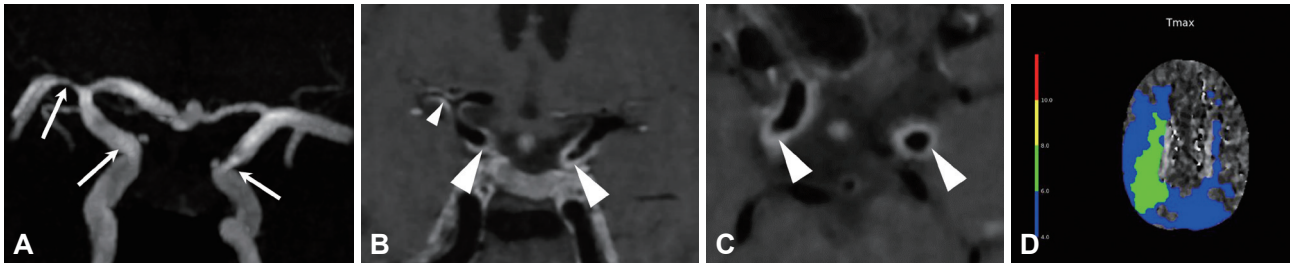

Fig. 1. Varicella-zoster virus vasculitis. A: Time-of-flight MR angiography reveals severe stenosis (indicated by arrows) in both internal carotid arteries and the proximal right middle cerebral artery. B and C: Coronal and axial contrast-enhanced vessel wall images demonstrate significant thickening and enhancement (arrowheads) in the corresponding vascular segments. D: Tmax map illustrates hypoperfusion in the vascular territories of both internal carotid arteries (blue areas), with critical hypoperfusion observed on the right side (green area). MR, magnetic resonance.

the medial layer and vessel dilation.[59] In a large sample of autopsy series from four brain banks, ischemic strokes in patients with HIV were attributed to inward remodeling and subsequent luminal narrowing,[60] and also extreme outward remodeling (dolichoectasia) of vascular walls.[61]

Certain fungal infections of the CNS can lead to stroke by direct infection or invasion of the vessel walls. These can occur in both immunocompetent and immunocompromised patients. Among these, yeast (e.g., *Cryptococcus* and *Candida species*) and hyphae-forming molds (e.g., *Aspergillus* and *Mucorales species*) have been implicated in stroke.[62]

RECENT ACUTE INFECTION AS A TRIGGERING FACTOR FOR STROKE

There is extensive evidence[63-82] that acute infections, even if mild, can precipitate ischemic stroke (Table 1). Paganini-Hill et al.[72] reported a case–control study showing an association between ischemic stroke and infections (and inflammatory events) during the preceding week or month; these were mostly respiratory infections that were associated with large-vessel atherothrombotic and cardioembolic strokes. Two case–control studies demonstrated links between recent infections and the risks of TIA and ischemic stroke.[65,76] Sebastian et al.[80] used the New York State Inpatient Database to study the associations of infection with all types of stroke (ischemic stroke, ICH, and subarachnoid hemorrhage). They reported that all types of common infections, including urinary tract infections, upper respiratory infections, skin infections, and abdominal infections, were specifically associated with subsequent ischemic stroke. Moreover, they showed that the stroke risk peaked closer to the time of infection (within 1–2 weeks), but that the increased risk lasted for up to 4 months. Another study found a similar increased risk of ischemic stroke that extended up to 12 months after the incident infection, especially in younger individuals.[78] In a case–crossover study of Dutch subjects aged 18–49 years, the risk of ischemic stroke increased by more than 14-fold when fever or flu-like illness occurred within 24 hours of the event.[82] Notably, these factors were found to potentially trigger the occurrence of all stroke subtypes other than small-vessel occlusion.

Children seem particularly prone to this increased stroke risk after even minor infections. In a population-based, case–control study of childhood arterial ischemic stroke, Hills et al.[83] reported that even typically minor infections were strongly associated with stroke. In children, this association occurred relatively early, typically 3 days or less from infection onset. In the Vascular Effects of Infection in Pediatric Stroke (VIPS) study, Fullerton et al.[84] reported a similar increased risk of preceding infections, especially in unvaccinated subgroups.

Data on the preventive effects of various vaccines are mixed. In population-based studies, herpes zoster vaccination in the elderly population had a protective effect for ischemic stroke,[85] whereas varicella vaccination in children showed no effect.[86] The large community-based 3-year prospective-cohort Community-Acquired Pneumonia, Acute Myocardial Infarction and Stroke (CAPAMIS) study had the primary aim of determining the effectiveness of the 23-valent pneumococcal polysaccharide vaccine (PPV23) against community-acquired pneumonia, acute myocardial infarction, and ischemic stroke in individuals aged at least 60 years. Vila-Corcoles et al.[87] found that the PPV23 was not effective in preventing cardiovascular events, and instead actually increased the thrombosis risk. Johnstone et al.[88] and Lavallée et al.[89] reported conflicting findings for the protective effect of influenza vaccination in reducing subsequent vascular events in patients with a high cardiovascular risk. However, a meta-analysis of 11 studies by Lee et al.[90] showed that vaccination against influenza did significantly lower the risk of any type of stroke, including ischemic stroke (odds ratio [OR]=0.77, 95% confidence interval [CI]=0.60–0.98). A subsequent case–control study found a modest reduction of the ischemic stroke risk with the influenza vaccine (OR=0.88, 95% CI=0.84–0.92) and no reduction of the stroke risk with the pneumococcal vaccine.[91]

COVID-19 AND STROKE

The COVID-19 pandemic has brought into sharp focus the multifaceted interactions between stroke risk and viral respiratory infections.[92] SARS-CoV-2, the virus that causes COVID-19, is a single-stranded RNA virus of the *Coronaviridae* family. The host angiotensin-converting enzyme 2 (ACE2), which is abundant in alveoli, is the receptor for virus particles entering host cells. In addition to the lungs, arterial and venous endothelial cells as well as the arterial smooth-muscle cells abundantly express this molecule. Neurons, astrocytes, and oligodendrocytes with ACE2 receptors can be directly infected by the virus and activate the neuroinflammatory response.[93-95]

In addition to viral-induced endothelialitis[96] potentially leading to thrombosis and cerebral infarction, other proposed mechanisms include a hypercoagulable state induced by systemic/local inflammation, the cytokine storm, and postinfectious immune responses such as infection-induced aPL or overproduction of neutrophil extracellular traps.[97,98] An autopsy brain study demonstrated neuroinflammation via the activation of endothelial cells, complement system, immune cells, astrocytes, and microglia, along with microthrombi in nine patients who died with COVID-19.[99] This has led to the identification of several serological biomarkers reflecting in-

Table 1. Studies of recent infections and ischemic stroke

Study	Design and location	Population	Interval between preceding infection and stroke	Association between infection and ischemic stroke	Comments
Syrjänen et al.[64]	Case-control study; Finland; single center	54 cases and 54 population controls	<1 month	RR=14.5, 95% CI=1.9-112.3	Respiratory infections (m/c)
Grau et al.[65]	Case-control study; Germany; single center	197 cases and 197 population controls	<1 week	aOR=4.6, 95% CI=1.9-11.3 (ischemic stroke and TIA)	Recent infections, primarily of bacterial origin. Patients aged 51-60 and 61-70 years as other significant variables
Bova et al.[66]	Case-control study; Germany; single center	182 cases and 194 controls with previous stroke	<2 months	OR=2.92, 95% CI=1.64-5.26	Respiratory and UTIs (more common)
Macko et al.[67]	Case-control study; USA; single center	37 cases, 47 community controls, and 34 hospitalized nonstroke patient controls	<1 week (infectious and inflammatory syndromes)	Prevalence of infection/inflammation was significantly higher in the case group than in either control group*	Upper respiratory tract infections (m/c)
Grau et al.[68]	Case-control study; Germany; single center	166 cases and 166 hospital controls	<1 week	OR=2.9 (95% CI=1.31-6.4) (ischemic stroke and TIA)	Respiratory tract infections (m/c). Infection increased risk of cardioembolism (OR=3.25, 95% CI=1.06-10.0) and tended to increase risk of artery-to-artery embolism (OR=7.0, 95% CI=0.86-57)
Nagaraja et al.[69]	Case-control study; India; single center	60 cases and 60 population controls	<2 weeks (mainly)	Infection in 26 cases and 6 controls (43.3% vs. 10%, $p<0.001$)	Respiratory tract infections (m/c)
Becher et al.[70]	Case-control study; Germany; single center	197 cases (ischemic stroke and TIA) and 197 population controls	<1 week	OR=4.33, 95% CI=1.78-10.51. Attributable risk of 0.15 (95% CI=0.09-0.21)	
Nencini et al.[71]	Case-control study; Italy; single center	93 cases and 200 (107 hospital and 93 community) controls	<1 month (infectious and noninfectious events)	1 month: OR=2.23, 95% CI=1.26-3.96 1 week: OR=2.45, 95% CI=1.11-5.39	Acute infectious event significantly increased risks of atherothrombotic (OR=5.72, 95% CI=2.14-15.25) and cardioembolic stroke (OR=3.02, 95% CI=1.20-7.63)
Paganini-Hill et al.[72]	Case-crossover design; USA; single center	233 cases and 362 outpatient controls	<1 month	No significant difference between the two groups*	Large-vessel atherothrombotic or cardioembolic stroke more common in patients with recent respiratory infection (<1 week) than in patients without infection (48% vs. 24%)
Zurrú et al.[73]	Case-control study; Argentina; single center	105 cases with atherothrombotic stroke and 354 outpatient controls	1 year	aOR=4.9, 95% CI=2.3-10.2	Respiratory tract infections were the most common type of infection at <3 months before an ischemic event, and more common in cases than control subjects (17% vs. 4%)

Table 1. Studies of recent infections and ischemic stroke (continued)

Study	Design and location	Population	Interval between preceding infection and stroke	Association between infection and ischemic stroke	Comments
Elkind et al.[74]	Case-crossover; USA; Cardiovascular Health Study	5,639 elderly population	<2 years as control period (hospitalization for infection)	14 days: aHR=3.9, 95% CI=1.9–7.9 30 days: aHR=2.4, 95% CI=1.3–4.4 90 days: aHR=2.4, 95% CI=1.6–3.4	
Dalager-Pedersen et al.[75]	Cohort study; Denmark; 3 databases	4,389 cases with community-acquired bacteremia, 43,831 population controls, and 21,893 hospitalized controls	<1 year community-acquired bacteremia	vs. population controls: 0–30 days: RR=25.82, 95% CI=16.72–39.89 31–180 days: RR=1.90, 95% CI=1.26–2.89 181–365 days: RR=0.97, 95% CI=0.58–1.59 vs. hospitalized controls: 0–30 days: RR=2.41, 95% CI=1.84–3.15 31–180 days: RR=1.25, 95% CI=0.82–1.91 181–365 days: RR=0.71, 95% CI=0.42–1.20	
Consoli et al.[76]	Prospective case-control study; Italy; multicenter	749 cases and 253 outpatient controls	<1 month	OR=4.09, 95% CI=2.10–7.95 Early previous infection (<7 days before event) and chronic infection due to *Chlamydia pneumoniae* increased risk of acute cerebral infarction (RR=2.12, 95% CI=1.26–3.58; and RR=3.69, 95% CI=1.13–6.88; respectively)	Respiratory tract infections (m/c)
Cowan et al.[77]	Case-crossover; USA; ARIC (Atherosclerosis Risk in Communities)	1,008 ischemic stroke cases	<2 years as control period (hospitalization for infection)	14 days: aOR=7.7, 95% CI=2.1–27.3 30 days: aOR=5.7, 95% CI=2.3–14.3 90 days: aOR=3.6, 95% CI=2.1–6.5	Higher aOR in thrombotic strokes for the 14-day period and cardioembolic strokes for the 43-day period
Boehme et al.[78]	Case-crossover; USA; California State Inpatient Database	37,377 ischemic and 12,817 hemorrhagic stroke cases	<1 year (sepsis)	<15 days: OR=28.4, 95% CI=20.0–40.1 16–30 days: OR=4.0, 95% CI=2.86–5.60 31–90 days: OR=2.53, 95% CI=2.07–3.09 91–180 days: OR=2.46, 95% CI=2.03–2.99 181–365 days: OR=2.59, 95% CI=2.20–3.06	
Boehme et al.[79]	Case-crossover; USA; California State Inpatient Database	36,975 ischemic stroke cases	<1 year (influenza-like illness)	<15 days: OR=2.83, 95% CI=1.86–4.47 16–30 days: OR=1.73, 95% CI=1.01–3.02 31–60 days: OR=1.68, 95% CI=1.13–2.51 61–90 days: OR=1.05, 95% CI=0.67–1.64 91–180 days: OR=1.23, 95% CI=0.95–1.59	
Sebastian et al.[80]	Case-crossover; USA; New York State Inpatient Databases and Emergency Department Databases	152,356 acute ischemic stroke cases	<1 year as control period	Different infection types (skin infection, UTI, septicemia, abdominal, and respiratory) were significantly associated with ischemic stroke	Strongest association with ischemic stroke was for UTI (OR=5.32, 95% CI=3.69–7.68) within the 7-day window

Table 1. Studies of recent infections and ischemic stroke (continued)

Study	Design and location	Population	Interval between preceding infection and stroke	Association between infection and ischemic stroke	Comments
Pak et al.[81]	Self-controlled case series; Australia; single center	4,557 patients with pneumonia	<2 weeks as risk interval and the control interval as 1 year before and 1 year after the risk interval	RIR=4.94, 95% CI=1.12–21.78	
Ekker et al.[82]	Case-crossover; Netherlands; multicenter	1,043 ischemic stroke cases and 103 young adults with ICH	<1 day (fever or flu-like disease)	Fever: RR=15.1, 95% CI=9.0–25.5 Flu-like disease: RR=15.2, 95% CI=9.7–23.8	Fever and flu-like illness as trigger factors for cryptogenic stroke, large-artery disease, cardioembolic stroke, and stroke of other determined cause, but not small-vessel disease

*Noninfectious inflammatory events were included.
aHR; adjusted HR; aOR; adjusted OR; CI, confidence interval; HR, hazard ratio; ICH, intracerebral hemorrhage; m/c, most common; OR, odds ratio; RIR, relative incidence rate; RR, relative risk; TIA, transient ischemic attack; UTI, urinary tract infection.

flammation and coagulation. Elevated fibrin D-dimer, lactate dehydrogenase, erythrocyte sedimentation rate, and CRP were demonstrated in COVID-19-associated ischemic stroke.[100,101] Some authors have asserted that increased fibrin D-dimer and aPL are associated with COVID-19-related stroke.[102,103] Fibrin D-dimer as a marker of COVID-19 coagulopathy is a notable predictor of poor outcome and mortality.[104]

Other respiratory infections such as influenza have long been associated with an increased stroke risk. A retrospective cohort study found that 31 of 1,916 patients with COVID-19 (1.6%, 95% CI=1.1%–2.3%) at two academic hospital centers had an ischemic stroke, while only 3 of 1,486 influenza patients (0.2%, 95% CI=0.0%–0.6%) had an ischemic stroke.[105] The stroke risk with COVID-19 infection remained markedly higher than with influenza infection after adjusting for several confounding factors including vascular risk factors (OR=7.6, 95% CI=2.3–25.2).

Based on a systematic review of 10 studies, Fridman et al.[106] reported that stroke occurred in 1.8% (95% CI=0.9%–3.7%) of COVID-19 patients. They also reported that large-vessel occlusions were common across all age groups and that the in-hospital mortality rate was higher in patients with stroke related to COVID-19 (34.4%). In-hospital mortality was also more common in older patients, especially in those with multiple comorbidities and severe respiratory symptoms. Underreporting that can occur due to mild cases not being hospitalized or severe cases being wrongly attributed to non-COVID-19 causes might result in underestimation of the risk of stroke due to COVID-19. A preventive effect of the COVID-19 vaccine on thrombotic events including ischemic stroke was found in a Korean nationwide registry-based study.[107] Acute ischemic stroke can also occur as a rare complication of the COVID-19 vaccine via thrombotic thrombocytopenia, especially for virus vector vaccines.[108]

THERAPEUTICS FOR INFECTION-ASSOCIATED STROKE

Infection-associated stroke may develop during or after a localized or systemic infection. However, even when the causality of a prior or current infection in the induction of acute stroke is suspected at the time of disease presentation, it is unlikely that an emergency-care provider would make special or atypical personalized diagnostic and treatment decisions. In addition, clinical trials,[109] observational studies,[110,111] and meta-analyses[112,113] have not proved the efficacy of specific treatments such as prophylactic antibiotics. At present, there are no data available from controlled clinical trials to suggest that published diagnostic and treatment protocols would improve patient outcomes in infection-associated acute

stroke. This may be attributed to the great heterogeneity of this patient population in terms of the types of infection (e.g., acute, chronic, active, previous, pathogens, local, and systemic), types of stroke, and the short window of opportunity for evaluating specific infection-related diagnostic considerations before emergency treatment is started to reduce or prevent irreversible brain injury. In addition, there are no established, high-quality data available to demonstrate the efficacy and safety of using fibrinolytic and other antithrombotic treatments in the presence of an active infection; however, there are also no high-quality data to prove the opposite. Therefore, the current treatment practice likely ignores whether an infection, past or present, has played a causal (etiological) role in the development of stroke in a particular patient. Based on review of the limited clinical trial literature in this topic, there appears to be no data to suggest that treatment of infection-associated stroke should be considered a separate category.

Some medical research over the past few decades have focused on the development of mechanistically novel and theoretically safe(r) antithrombotic and anti-inflammatory/cytoprotective agents. Examples of this new direction include enhancement or modification of the antithrombotic and/or cytoprotective protein C system or therapeutic anticoagulation by inhibiting the contact activation of blood.[114-120] Immunomodulatory drugs can be considered as a new treatment option in that neuroinflammatory response plays an important role in infection-related stroke. Targeting specific components of the inflammatory cascade has shown positive results in several randomized controlled studies. Interleukin-1 (IL-1) family has been considered important mediators of the innate immune response.[121] Of them, IL-1α, IL-1β and IL-1 receptor antagonist (IL-1Ra) have been major targets for the development of new therapies. The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) showed that an anti−IL-1β antibody in patients at high risk for atherosclerotic events can decrease cardiovascular events by 15%.[122] In the VCU-ART2 and VCU-ART3 (Virginia Commonwealth University-Anakinra Remodeling Trials 2 and 3, respectively),[123,124] anakinra, a recombinant human IL-1Ra, was reported to reduce systemic inflammation and the risk of the composite endpoint of death or heart failure in patients with acute myocardial infarction; it also reduced plasma inflammatory markers including interleukin-6 and CRP in two randomized controlled trials.[125,126] Regarding ischemic stroke, however, the beneficial effect on clinical outcomes was observed in only one study.[125] This implies that the clinical application of these materials can be difficult due to the dual role of neuroinflammation from injury to repair after ischemic damage.[127] There have also been approaches to alleviate inflammation. In two randomized controlled trials, low-

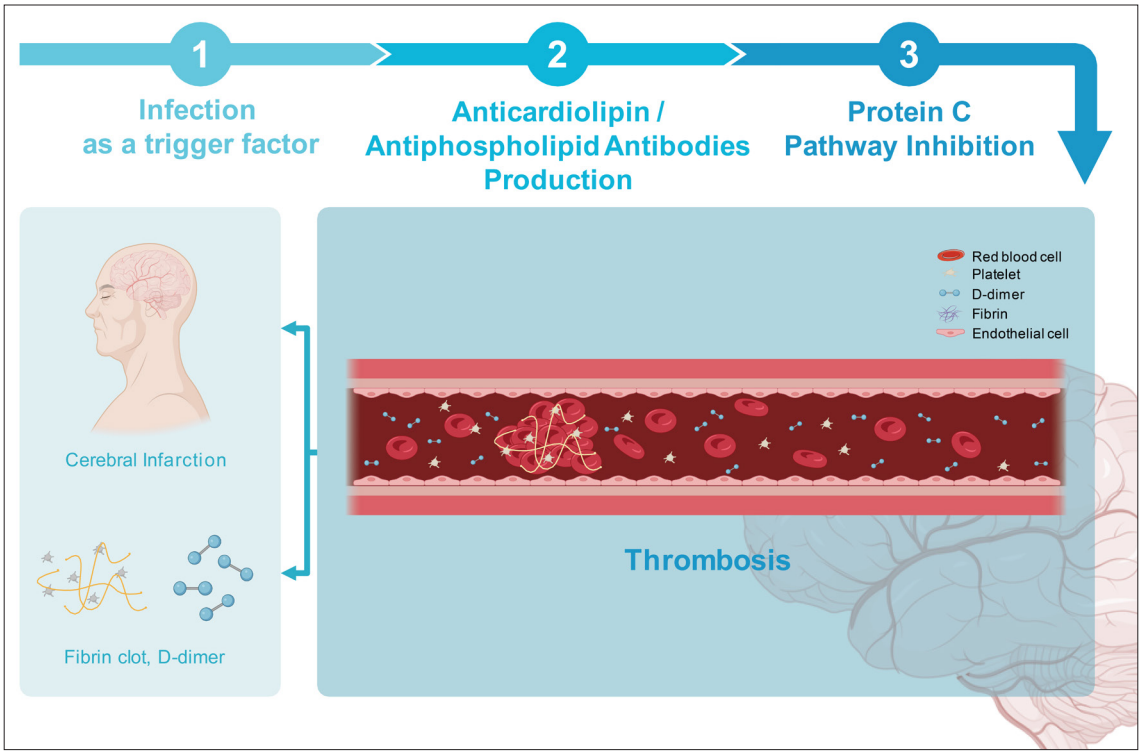

Fig. 2. Proposed pathway for ischemic stroke provoked by infection. In this mechanistic pathway, infections generate antibodies directed against cardiolipin or phospholipid, which then impair the protein C system leading to thrombosis, brain infarction, and subsequent generation of fibrin D-dimer.

dose colchicine, an old drug with new potential uses, reduced recurrent vascular events in patients with coronary artery disease.[128,129] There is hope that these treatments can be applied to infection-related stroke.

CONCLUSION

There remains a critical question for stroke neurology regarding the nature of the relationship between infection and stroke. That question is: When is an infection that precedes a stroke acting as a trigger for the cerebrovascular event? Alternatively, when is an infection preceding a stroke simply an incidental finding and of no pathogenic significance? At the present time, there is no definitive way to make this distinction. Moreover, there are additional aspects that require analysis, such as determining associations of stroke subtypes with infection, identifying specific infectious organisms causing stroke, and delineating mechanisms of the stroke–infection relationship based on stroke subtypes.

The most likely answer to this question requires the establishment of confirmed biomarkers for infections relevant to the pathogenesis of a specific stroke. And while there are no such established biomarkers, there are some plausible candidates that have emerged from studies performed in the early 1990's to the era of COVID-19. The most-notable candidates for identifying the pathogenic infection preceding stroke are fibrin D-dimer and aCL/aPL.

Ameriso et al.[25] first identified elevated levels of fibrin D-dimer and aCL as biomarkers of infection-associated ischemic stroke, and some studies during the COVID-19 pandemic have tended to confirm this association.[130-135] Given the demonstrable effects of aPL on the endogenous protein C system, a plausible scenario for infection-triggering stroke implicates antiphospholipid antibody-mediated inhibition of the anticoagulation effects of the protein C system. The consequence of protein C inhibition would then manifest itself as fibrin generation producing thrombo-occlusion of the brain vasculature, leading to infarction with subsequent clot lysis producing elevated levels of fibrin D-dimer (Fig. 2). At the present time, this scenario remains the most-promising conceptual framework for identifying the pathogenicity of infections related to ischemic stroke. However, the specificity of the combination of elevated fibrin D-dimer and aCL has yet to be demonstrated. More-extensive confirmation of these biomarkers will pave the way for targeted therapeutics of the challenging syndrome of infection-associated stroke.

Availability of Data and Material

Data sharing is not applicable to this article as no datasets were generated or analyzed during the study.

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Conflicts of Interest

AG is an employee and shareholder of Aronora, Inc., a company that has been developing antithrombotic agents.

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