Stroke

TOPICAL REVIEW

Acute Viral Illnesses and Ischemic Stroke

Pathophysiological Considerations in the Era of the COVID-19 Pandemic

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ABSTRACT: The severe acute respiratory syndrome coronavirus 2 or coronavirus disease 2019 (COVID-19) pandemic has raised concerns about the correlation with this viral illness and increased risk of stroke. Although it is too early in the pandemic to know the strength of the association between COVID-19 and stroke, it is an opportune time to review the relationship between acute viral illnesses and stroke. Here, we summarize pathophysiological principles and available literature to guide understanding of how viruses may contribute to ischemic stroke. After a review of inflammatory mechanisms, we summarize relevant pathophysiological principles of vasculopathy, hypercoagulability, and hemodynamic instability. We will end by discussing mechanisms by which several well-known viruses may cause stroke in an effort to inform our understanding of the relationship between COVID-19 and stroke.

Key Words: coronavirus ■ ischemic stroke ■ pandemic ■ syndrome ■ viruses

A wide range of viruses has been linked to an increased risk of ischemic stroke.[1] In many cases, the infection occurs in the periphery with no detectable virus in the central nervous system (CNS), and yet stroke incidence is elevated. Indeed, case-control studies have consistently demonstrated an association between a preceding systemic infection and stroke, often with a time frame of several days from onset of infectious symptoms to stroke.[2–5] In such cases, the predominant pathogenic mechanism is thought to result from systemic immune activation, which in concert with associated hypercoagulability or endothelial dysfunction may cause vascular injury or formation of thromboemboli. In contrast, other viruses such as the herpesviruses can invade the CNS and directly infect blood vessels.[6] In such scenarios, the pathogenic mechanism of stroke may be more straightforward to explain, although CNS invasion does not preclude an additional role of systemic immune activation in stroke pathogenesis (Figure 1).

VIRUSES AND INFLAMMATION

Before turning to pathophysiological mechanisms by which viruses may induce stroke, it is worth considering how the immune system of the host responds to viral infection. Viruses are obligate intracellular parasites that invade the cells of the host to survive and replicate. Most human viruses only replicate in certain host tissues as a result of tissue-specific distribution of viral receptors.[7] Once viruses attach to cellular receptors and gain entry into cells, they use a combination of virally encoded proteins and host cell machinery to replicate within cells. Many viruses then induce cytolysis to promote release of new infectious viral particles. During the viral life cycle, viruses interact with the host immune system in numerous ways and encounter multiple innate and adaptive defenses that serve to combat the infection.[8]

The effectiveness of the immune response to viruses depends in large part upon rapid detection of viral components by the host's innate immune system. Viral constituents that are recognized include capsid proteins, glycoproteins on the viral surface, and nucleic acids, and together these are termed pathogen-associated molecular patterns. Pathogen-associated molecular patterns are detected by host PRRs (pattern recognition receptors) such as Toll-like receptors and retinoic acid-inducible gene I–like receptors, which allow the host to distinguish viral from host components.[9] Sensing of viral

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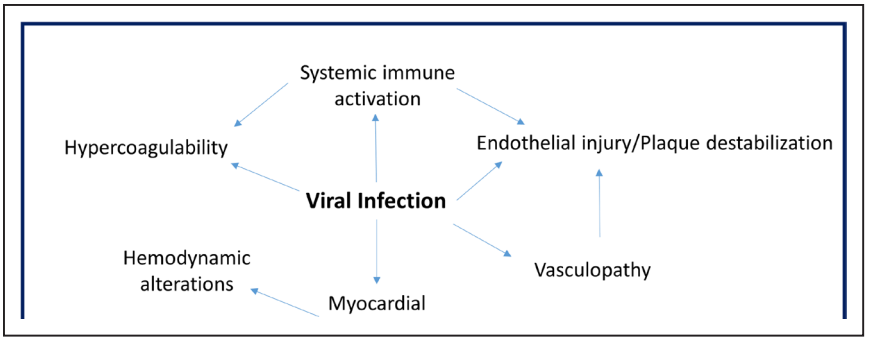

Figure 1. Schematic of potential mechanisms by which viral infections can cause ischemic stroke.

pathogen-associated molecular patterns by PRRs triggers signaling cascades such as stimulator of interferon genes that lead to the production of a myriad of host defense molecules, including IFNs (interferons) and proinflammatory cytokines.[10] These compounds can directly inhibit viral replication (eg, type 1 interferons such as IFN-α and IFN-β), enhance innate immune responses by, for example, recruiting myeloid cells, such as neutrophils and macrophages, and assist in inducing adaptive immune responses.[8,11–13] Adaptive immune responses, whose effectors are T and B lymphocytes, are particularly important for promotion of viral clearance. Thus, these immune cascades are indispensable for not only mounting an effective initial antiviral response but also in ultimately terminating the viral infection. Importantly, they are tightly controlled with respect to amplitude and duration due to a multitude of feedback mechanisms that serve to titrate the response. Unrestrained activation in the setting of certain infections or genetic abnormalities can result in marked systemic inflammation with deleterious consequences to the host.[14,15]

In the case of direct viral infection of the CNS, neural cells including microglia, astrocytes, and neurons collaborate with immune cells to contribute to antiviral immune responses. Microglia are a key innate immune mediator in the CNS and assist in control of viral replication via production of antiviral cytokines and phagocytosis of virus-infected neurons.[16] Astrocytes can be activated by a variety of mechanisms, including direct viral infection, release of viral particles, death of neighboring neurons, or via proinflammatory cytokines released by microglia.[17,18] In the setting of flaviviral infection, for example, astrocytes produce type I interferons and restrict viral spread.[19] Moreover, activated astrocytes can regulate the adaptive immune response through upregulation of major histocompatibility complex class I molecules,[20,21] thus also contributing to viral clearance. It has also been recognized that neurons can produce type I interferons and that they express major histocompatibility complex class I molecules, thus actively participating in antiviral defenses.[22,23] In addition, all 3 cell types—astrocytes, microglia, and neurons—can produce chemokines that recruit leukocytes to the CNS, thus furthering the innate immune response and assisting in development of the adaptive immune response.[17]

GENERAL PATHOPHYSIOLOGICAL MECHANISMS OF VIRAL INFECTIONS AND STROKE

Vasculopathy

Vasculopathy is a general principle to describe any condition that affects blood vessels. This may include inflammatory, hemostatic, metabolic, or genetic disorders. Several mechanisms have been proposed in the association of systemic infections and intracranial vasculopathy. The effect on the blood vessel may be due to direct vascular invasion, immune complex deposition into the endothelium, inflammation, or immune modulation with activation of T lymphocytes changing the surface milieu of the endothelial wall.[24,25] The systemic vascular responses can lead to vessel wall inflammation, direct change in the shape of the blood vessel wall, rupture of atherosclerotic plaques, or destabilization of cardiovascular conditions ultimately leading to a variety of clinical conditions, including stroke.

Infectious agents with direct tissue tropism to the vascular endothelium cause structural changes in the vascular wall. This can result in direct vascular damage via a variety of mechanisms, including the example of binding of viral components to the endothelial cell resulting in activation of adhesion molecules (eg, P-selectin) with subsequent release of proinflammatory cytokines and chemoattractants.[26] In this example, the host vessel can develop roughing of the endothelial or formation of mycotic aneurysm. There are other notable examples of direct causation of vascular wall damage, including the hepatitides where immune complexes synthesized in response to infection can be found in the blood vessel wall causing vasculitis. In such cases, medium-sized vessels are typically affected, potentially leading to polyarteritis nodosa-like illnesses.[27,28] In other examples, shared epitopes between the pathogen and host can upregulate heat shock proteins and stimulate lymphocytes that mediate destruction of the vessel wall via autoreactive T cells. In the case of giant cell arteritis, viruses such as varicella zoster have been associated with the vasculopathy that is potentially triggered by direct infection or the immune response from antigen deposition in the blood vessel wall.[29,30] Overall, viral infection and the

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inflammatory changes caused in the vaso vasorum may accelerate the development of atherosclerosis or lead to destabilization of existing plaques, development of a prothrombotic state, and onset of ischemic stroke.[31,32]

Numerous hypotheses have been put forth for the causes of indirect vasculitis. One increasingly popular consideration is that change in the renin-angiotensin system via alterations in ACE (angiotensin-converting enzyme) may be a potential contributor to vasculitis. Angiotensin II is the primary effector molecule of the reticular activating system and is a proinflammatory modulator that triggers and perpetuates immune responses.[33] ACE-2, a homolog of ACE degrades angiotensin II to angiotensin. Angiotensin is well known for its vasodilating and antithrombotic properties. It has been proposed that antibodies to ACE-2 leads to vasculopathy[34] and vasculitis susceptibility in a series of studies of ACE polymorphisms.[33]

Inflammation and Atheromatous Plaque

Atheroma development and destabilization are 2 processes that are directly impacted by inflammation. Inflammation may generate atheroma development which eventually can contribute to disturbed cerebral blood flow. However, in the setting of viral infection, it is the destabilization and eventual plaque rupture that require attention.[35] Various mechanisms have been proposed to explain the relationship between systemic inflammation and plaque rupture, including expansion of the atheromatous plaque and direct enzymatic degradation of the cap.[25,26] The systemic inflammatory reaction and recruitment of blood immune cells may result in dynamic expansion in cholesterol when crystalizing from a liquid to solid state with the potential for sharp crystals to perforate the fibrous cap.[36] Alternatively, the inflammatory cytokines and proteases may lead to degradation and direct thinning of the atheromatous plaque with eventual plaque rupture.[37] In either scenario, plaque rupture leads to turbulence in blood flow in that region and a highly thrombogenic site.

Thrombosis, Hypercoagulability, and Viral Infections

As we conceptualize the origination and propagation of venous thrombosis in the setting of acute viral infections, one of 3 factors is often present: stasis, hypercoagulability, and changes in the blood vessel wall (the so-called Virchow triad). Homeostatic coagulation is an intricate balance between procoagulant and anticoagulant mechanisms and disruption of those finely tuned systems can lead to bleeding, abnormal clotting, or both.[38] The endothelium is a critical contributor to this process.[39] Acute viral illness can disrupt any of the homeostatic processes that govern those activities directly or indirectly via changes in the vessel wall integrity, changes in platelet function, triggering of acute phase reactants, or activation of the coagulation cascade, leading to either thrombosis or hemorrhage; here we will focus on the former.

Platelets are the key contributor to primary hemostasis, and their function can be directly altered by viral infection. Indeed, the binding of viruses to platelets results in platelet activation, resulting in exposure of P-selectin on the platelet surface.[38] This can trigger activation of platelet-leukocyte aggregates and endothelial cells with associated increased expression of molecules, such as von Willebrand factor. This process, in turn, induces aggregation of platelets and fibrin as an acute phase reactant, which contributes to thrombus initiation and growth.[40]

Secondary hemostasis or changes in the coagulation cascade are largely maintained by inhibitory mechanisms and can be influenced by active viral infection at a variety of points in the process.[41] Tissue factor is the main initiator of the coagulation cascade that leads to thrombin formation and is located in the subendothelium, leukocytes, and platelets. Tissue damage leads to activation of tissue factor (extrinsic system) triggering the coagulation cascade to form small amount of Factor X and thrombin. This, in turn, feeds back on the intrinsic system to activate Factor XI which eventually triggers a very robust activation of factor X with a large amount of thrombin produced followed by large amounts of fibrin clot. The overall activity of the coagulation cascade is controlled by circulating anticoagulant factors such as tissue factor pathway inhibitor which decreases extrinsic pathway activity, activated protein C/S which downregulate factor VIII and Factor V, and antithrombin/heparin cofactor II to reduce factors like thrombin and activated factor X.[38] Additionally, an intact fibrinolytic pathway that requires release of tissue-type plasminogen activator from the endothelium hydrolyzes fibrin to degrade formed fibrin strands. Clotting events increase when the balance is tipped toward procoagulant forces, activated platelets, increased thrombin formation, and impaired breakdown of fibrin clot.

In the setting of viral infections, changes in the blood vessel wall can perpetuate thrombosis. These changes can occur via (1) the inflammatory response: complement attacking the endothelium that upregulates clotting factors and damages the endothelial wall; and (2) directly invasion by the virus. Many viruses—in particular respiratory viruses, such as influenza, parainfluenza, and adenovirus—along with herpesviruses can infect endothelial cells, thus directly causing endothelial cell activation and promoting hypercoagulability. Viral mechanisms of endothelial activation include altering the composition of exposed phospholipids, direct generation of thrombin formation on the surface of endothelial cells initiated by viral components, and increasing available binding sites for inflammatory cells, including granulocytes and platelets, that can, in turn, produce procoagulant cytokines.[42–45]

Activation of the endothelium can result not only in hypercoagulability but can also contribute to furthering of cytokine production, thus leading to further inflammation and hypercoagulability. A notable example is that of influenza virus, where in an animal model endothelial cells were found to elaborate numerous proinflammatory mediators, including CCL2, CCL5, and CXCL10, that contribute to the systemic proinflammatory response.[46] In some animal models focused on select viral infections, fibrin-rich platelet aggregates that are associated with neutrophil extracellular traps are released by activated leukocytes triggering hypercoagulability and a hematologic state that further damages the endothelium.[47] This initiates a perpetuating cycle of hypercoagulability, progressive occlusion of microvasculature, and increased risk for sequential organ failure through large artery and small vessel mechanisms.

Other Physiological Considerations for Secondary Stroke Associated With Viral Infection

Infection, inflammation, and changes in hypercoagulability can have systemic effects including the propensity to increase hemodynamic and cardiac events.[48–50] Taken individually or together, many of the above-described processes can lead to changes in cardiac function. Many viruses, including adenovirus, are commonly associated with myocarditis or acute injury to the myocardium which increases risk for cardioembolic event.[48] In the setting of myocarditis, the myocardium is enlarged and pumping is impaired, leading to. This increased risk for cardioembolic. In the setting of viral illnesses, consideration of superinfection, with *Streptococcus pneumonia* or *Staphylococcus aureus*, is also important as secondary, bacterial infection can occur raising the risk of endocarditis and embolic stroke.[51]

In addition to hypercoagulability, metabolic sequelae of acute viral infection or hemodynamic changes with sepsis secondary to the viral infection may include hemodynamic fluctuation due to dehydration and alterations in intravascular volume.[52] As one example, dehydration can occur due to insensible losses from fever, diarrhea, or poor fluid intake related to malaise and anorexia. Patients with vascular risk factors like diabetes may be especially vulnerable since infection may worsen hyperglycemia leading to additional dehydration associated with a hyperglycemic state.[53] Dehydration contributes to a prothrombotic states and may destabilize several vascular risk factors, such as atrial fibrillation, potentially leading to increased risk for stroke.[54] Additionally, dehydrated patients who demonstrate blood pressure fluctuations or become orthostatic may suffer changes in cerebral perfusion pressure and infarction especially when those hemodynamic fluctuations exceed the autoregulatory capacity of the individual.[55,56] Patients with stroke who are in a volume contracted state at the time of stroke demonstrate worsened functional outcomes.[57] When superimposed on a background of baseline vascular risk factors and the presence of atherosclerotic disease, this type of physiological change in itself may contribute heavily to the timing of stroke in proximity to viral illness.

Finally, on a more practical level, malaise and anorexia common with acute viral syndromes may lead to the disruption of daily prescribed medications that can destabilize comorbid vascular conditions or to the addition of over the counter medications to treat those symptoms. Over the counter medications, such as nasal decongestants and cough suppressants, often taken to symptomatically treat viral infection, deserve attention when considering the relationship between acute viral infection and stroke. Many of these medications contain vasoactive substances like phenylephrine and other sympathomimetic agents. Use of these medications has been linked to destabilized hypertension, ischemic stroke, and intracerebral hemorrhage. These medications may have a more direct consequence on vasomotor tone and have been associated with the onset of reversible cerebral vasoconstriction syndrome.[58]

Taken together, acute viral illnesses may contribute to a variety of stroke subtypes. Large vessel occlusion or multifocal stroke may occur in settings of bacteremia, cardiac dysfunction, and arrhythmias leading to cardioembolic. Hypercoagulability can cause large vessel occlusion or small vessel stroke. Endothelial changes can cause thrombosis of large or small vessels. Dehydration and hypercoagulable states might lead to venous sinus thrombosis. In general, prolonged critical illness and immobility may lead to stasis, disruption of the Virchow triad and increased risks for venous thromboembolism. A clinician caring for patients in the setting of acute viral illness should consider stroke when a sudden change in neurological exam occurs in traditional vascular patterns or in the setting of more diffuse but sudden changes. Other associated symptoms such as fever, elevation in inflammatory markers like the erythrocyte sedimentation rate, absence of existing vascular risk factors, and immunocompromised status of the patient would raise the suspicion for infection as the potential cause of the stroke.

PATHOPHYSIOLOGICAL MECHANISMS IN SPECIFIC VIRAL INFECTIONS: LESSONS LEARNED AND EXTRAPOLATION TO COVID-19

Varicella-Zoster Virus

Primary infection by the varicella-zoster virus (VZV), a common occurrence worldwide, results in the typically self-limiting disease varicella (chickenpox). Following

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primary infection, the virus establishes lifelong latency in sensory ganglia via mechanisms that have yet to be fully characterized. Viral reactivation can occur in the setting of immunosuppression or aging.[59,60] When reactivation proceeds peripherally, the painful rash of zoster occurs, while when central propagation occurs the virus can cause encephalitis, myelitis, and stroke.[61–64] In an effort to prevent VZV-associated illness, most children in the United States receive a live attenuated VZV vaccine, which is 80% to 85% effective in preventing chickenpox; however, it, too, can establish latent infection and be reactivated since neurovirulence is retained.[65] Notably, VZV-associated stroke does not solely occur following viral reactivation but can also occur in the setting of acute chickenpox.[66] Strokes following VZV infection or reactivation can occur in the acute or subacute phases or may occur as a chronic, recurrent process. The pathogenesis, which likely depends, in part, upon the time course following infection, may involve multiple processes alone or in combination, including systemic hypercoagulable state, in situ thrombosis, or vasculitis.[67–69] The latter is the most well-recognized phenomenon, and typically occurs weeks to months following infection and reactivation, although the timing can be quite variable (Figure 2).[70]

Humans are the only natural host for VZV, and the restricted species specificity has defied efforts to develop a robust animal model of infection that recapitulates all phases of disease.[71,72] As a result, the pathogenesis of VZV vasculitis has largely been elucidated from examination of arteries of infected subjects and in vitro studies of primary human cerebrovascular cells infected with VZV. These studies, while informative, are notably limited in scope. Immunohistochemical analysis of cerebral arteries from 3 patients with virologically confirmed VZV vasculitis demonstrated the presence of VZV antigen in the adventitial layer early in infection and in the media and intima later in the course of the disease.[73] This pattern is consistent with transaxonal spread of the virus from trigeminal ganglia to the vessel adventitia followed by transmural spread. Characteristics of VZV infected arteries include disrupted internal elastic lamina, thickened intima composed of myofibroblasts, and a paucity of smooth muscle cells, all of which may contribute to disruptions in integrity of the vessel wall. Overt inflammation of the blood vessels is often described, with neutrophils, B and T lymphocytes, and macrophages seen. Transmural granulomatous inflammation with multinucleated giant cells is the predominant pattern, and less commonly, there is a frank necrotizing arteritis; rarely a noninflammatory thrombotic occlusion in the setting of intimal proliferation is seen.[68,74] Cerebrospinal fluid studies from 30 patients with virologically confirmed VZV vasculitis demonstrated increased IL (interleukin)-6, IL-8, and MMP (matrix metalloproteinase) -2, all of which could play a role in inflammatory damage to the vascular wall.[75]

The presence of neutrophils in early VZV vasculitis in the adventitia is of interest since they can produce reactive oxygen species in the setting of infection, thereby triggering vascular remodeling.[76] Secretion of neutrophil-derived elastases and matrix metalloproteinases can result in loss of blood vessel integrity via breakdown of the extracellular matrix.

Recent in vitro work suggests that the centripetal spread of the virus from adventitia to intima may occur via microparticle containing VZV virions.[76,77] Human brain adventitial vascular fibroblasts infected with VZV were found to release microparticles containing VZV virions to neighboring cells, including other human brain adventitial vascular fibroblasts as well as endothelial cells, resulting in transmission of infection. Importantly, the microparticle-induced endothelial infection was associated with markers of endothelial activation and inflammation, including increased IL-6, IL-8, TNF (tumor necrosis factor)-α, and reactive

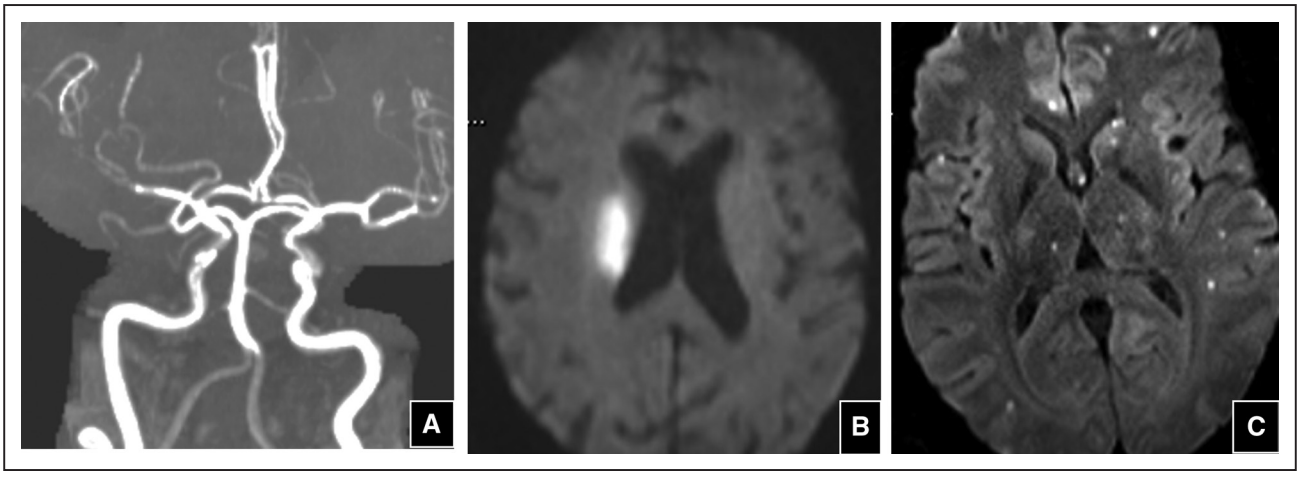

Figure 2. Select patterns of vasculopathy and ischemic stroke in varicella-zoster virus (VZV) infection.
A, Magnetic resonance angiogram demonstrating vasculopathy involving the right middle cerebral artery territory in the setting of acute VZV infection. **B**, Diffusion-weighted imaging (DWI) sequence demonstrates deep region of restricted diffusion in acute VZV infection. **C**, Scattered areas of restricted diffusion on DWI imaging in the setting of subacute VZV infection.

oxygen species production. In addition, human brain adventitial vascular fibroblasts infection was associated with the transformation of adventitial fibroblasts to myofibroblasts, thus potentially contributing to arterial remodeling. Notably, in the same study, VZV-containing microparticle complexes were also detected in the circulation of children with VZV vasculitis, although the study sample was quite small.

Recent work has also demonstrated the presence of VZV antigen in the adventitia of temporal arteries of patients with giant cell arteritis, raising the possibility of a pathogenic role for VZV in giant cell arteritis.[76] However, uncertainty remains and more work needs to be done to substantiate a potential role of VZV infection in the pathogenesis of giant cell arteritis.[78]

Common Respiratory Viruses

Several respiratory infections have shown ability to propagate in the CNS either by direct invasion or hematologic spread. While bacterial respiratory diseases more commonly cause direct invasion of the blood vessels; for example, *Mycobacterium tuberculosis* leading to granulomatous changes and fibrinoid necrosis, several series suggest that viral respiratory pathogens, such as Parvovirus B19, may also have a role in increased stroke risk due to arteriopathy.[1,79] Other studies do not show increase in stroke risk in association with any single pathogen but instead considers the infectious burden when assessing the relationship to stroke.[80] In general, inflammation is thought to be a primary mechanism. In a large prospective series including 19 063 patients with stroke, respiratory tract infection in the prior 3 days was associated with 3.19 increased incidence ratio for stroke (95% CI, 2.81–3.62).[81] We will discuss influenza as a model case since it is common and has both animal and population-level data.

There are data to suggest that influenza-like illnesses are associated with an increased risk of incident stroke. In one large cohort study, 554/36 975 ischemic stroke patients had at least one influenza-like syndrome with the highest odds of stroke if the flu-like syndrome occurred in the preceding 15 days (adjusted odds ratio, 2.88 [95% CI, 1.86–4.47]).[82] To elucidate the mechanisms of the relationship to poor outcome after viral infection and stroke, researchers infected mice with human influenza A then occluded the middle cerebral artery to induce stroke.[83] They found significantly increased expression of neutrophils, IL-1β, monocytes chemoattractant protein 1, MIP (macrophage inflammatory protein)-2, and TNF in the brains of stroke mice who were coinfected with influenza A, concluding that influenza aggravates stroke pathophysiology out of proportion to fever or hypoxemia.

Coronavirus Disease 2019

There is a suggestion that coronavirus disease 2019 (COVID-19) infection increases risk for stroke, but this association is yet unproven.[84] To date, published series are small and comorbid conditions cloud the ability to ascertain causality.[85–88] Larger, population-based studies will be required to determine if the association between COVID-19 and stroke is different as compared to the relationship between other acute viral illnesses and stroke. In a cohort study,[84] researchers compared stroke incidence in 1916 patients hospitalized with COVID-19 infection during a 2-month period to the 1486 patients hospitalized with influenza A/B over a 2 year period. Basic demographics were relatively similar between the 2 groups, with the exception of higher numbers of patients with hypertension in the COVID-19 group. In this cohort, there was a 7.6 (95% CI, 2.3–25.2) increased odds of acute ischemic stroke in the COVID-19 group compared with those admitted with influenza after adjustment for age, sex, and race. Although there are notable methodological issues limiting broad generalization, this study gives us a first insight to the behavior of COVID-19 and stroke as compared with other more well-known viral infections and raises the possibility that COVID-19 infection carries a stronger association with stroke.

How might COVID-19 infection increase the risk for stroke? Several of the above mechanisms, including hypercoagulability, may be at play when considering the relationship between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and stroke risk.[89] In its simplest pathophysiological explanation, changes in the cardiovascular system including intravascular volume changes in the setting of critical infection with COVID-19 may increase atrial fibrillation and cardioembolic potential, or more directly lead to changes in cerebral perfusion pressures that exceed the autoregulatory capacities of this population.[90] This explanation will most likely apply to those patients who have comorbid illnesses known to accelerate intra and extracranial disease and superimposed critical illness. Venous thromboembolism may be explained conceptually through the Virchow triad especially in a population of critically ill, older adults who are immobile and at high risk for both stasis and activation of inflammatory mediators that increase procoagulant forces and the likelihood of more clotting events. Alternatively, expression of ACE-2, the receptor for coronavirus entry, in both venous and arterial endothelium raises the possibility of direct viral effects on endothelial cells with resultant increased propensity for ischemic stroke.[91,92]

Vascular changes with the propensity to cause stroke are not confined to the cerebrovascular system. It has been recently suggested that downregulation of ACE-2 leading to both arteriopathy and thrombosis may play a central pathophysiological part in the development of stroke during SARS-CoV-2 infection.[93,94] ACE overactivation and ACE-2 underactivation are involved in lung injury and influences the renin-angiotensin system, which has a variety of vascular effects. ACE-2 underactivation

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results in a higher formation of angiotensin II which can lead to prothrombotic state and vasoconstriction which both conspire to cause cerebral ischemia.[93] A unifying mechanism like this one is biologically reasonable and could explain several comorbid conditions seen in patients with SARS-CoV-2 infection, although this clearly requires additional investigation.

Much attention has also been focused upon the marked immune dysregulation resulting in hypercytokinemia, or cytokine storm in both the periphery and the CNS that has been observed in some COVID-19 affected individuals. Patients admitted to the intensive care unit with SARS-CoV2 infection had higher levels of multiple proinflammatory mediators in their serum, including IP10 (interferon γ-induced protein 10), MCP-1 (monocyte chemoattractant protein-1), MIP1A (macrophage inflammatory protein 1α), and TNF-α compared with those not admitted to the intensive care unit.[95] Moreover, those who died of COVID-19 complications had higher serum levels of proinflammatory molecules, including IL-6 and C-reactive protein.[96] An early imbalance between proinflammatory and antiinflammatory molecules has been postulated to lead to a cascade of events that culminates in cytokine storm. Levels of classic proinflammatory cytokines, including TNF-α and IL-1β, along with chemotactic cytokines, such as IL-8 and MCP-1, rise promptly in the condition and facilitate a sustained increase in IL-6.[97] IL-6 then activates the Janus kinase-signal transducer and activator of transcription pathway, leading to synthesis of additional proinflammatory molecules as well as IL-6 itself, thus resulting in a feed-forward loop of inflammation.[98] Notably, deficiency of type I IFN responses may contribute to the observed hypercytokinemia. Indeed, in those with severe disease, type I interferon responses were diminished while proinflammatory cascades were upregulated; moreover, autoantibodies against type I IFNs or genetic deficiencies in type I IFN pathways have been observed in individuals with severe disease.[99–101] Of interest given the preponderance of severe disease in older age is that the immune changes that occur during aging result in alterations in humoral- and cell-mediated responses, as well as impaired clearance of infected and dying cells, that may predispose the elderly to unrestrained inflammation.[102] The observed hypercytokinemia is associated with low levels of cytotoxic T cells, which may contribute to reduced viral clearance and further propagation of the inflammatory response.[103] The consequences of runaway hypercytokinemia can be disastrous and may include endothelial dysfunction, vascular damage, and hypercoagulability. Indeed, the observed endotheliitis in patients with severe COVID-19 infection,[104] and the finding of elevated D-dimer in the majority of case series may, in some cases, be directly related to hypercytokinemia.[89] Endothelial exocytosis could trigger changes in the local milieu altering the balance of local clotting factors, specifically von Willebrand factors and Factor VIII. Thus, it has been posited that the inflammatory and clotting factor imbalance leads to a perpetuating cycle of microvascular thromboses in a variety of end organs.[105]

Additional considerations about the neurotropic potential of this novel virus are yet unknown. The family of human pathogenic coronaviruses has been shown to be capable of invading the CNS in both animal models and humans.[106,107] Entry of the pathogen through the cribriform plate with potential direct spread has not yet been demonstrated, however, it has been suggested that such a pattern of SARS-CoV-2 dissemination could cause changes in the posterior circulation.[106] While more data will be needed to definitively answer this question, it is our opinion that neuroinvasion by SARS-CoV-2 seldom occurs—particularly in immunocompetent individuals—and thus such a mechanism is unlikely a major contributor to stroke in the setting of COVID-19.

CONCLUSIONS AND FUTURE DIRECTIONS

Viral infections can impact both the periphery and the CNS, leading to increased risk of stroke. The importance of understanding basic pathophysiological concepts related to acute viral illness and stroke has been highlighted by the potential relationship between COVID-19 and stroke. Future studies will need to focus on a variety of mechanistic hypotheses underlying a potential association between COVID-19 and stroke onset. These will include studies to identify endothelial injury and hypercoagulable states at a micro and macro level. Careful assessment of inflammatory markers and the potential development of prothrombotic autoantibodies will need to be performed. Studies including vessel wall imaging would be useful to understand the frequency of vasculopathy in this population. Imaging studies would allow for better quantification of the various patterns of stroke in this population, however, may be challenging to obtain in a population of critically ill patients with infectious potential and strict isolation precautions. Characterization of well-defined cohorts of patients with careful consideration of confounders will aid in elucidation of populations at risk, which can subsequently be targeted in treatment trials. At a population level, an epidemiological study of asymptomatic or mildly ill patients with COVID-19 would assist the understanding of the unique association between the SARs-CoV-2 virus and stroke by eliminating confounding factors of critical illness. Finally, population-based studies comparing patients infected with COVID-19 to other viral illnesses that lead to critical respiratory illness will help to determine whether there is a unique association between COVID-19 and stroke.

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ARTICLE INFORMATION

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REFERENCES

1. Fugate JE, Lyons JL, Thakur KT, Smith BR, Hedley-Whyte ET, Mateen FJ. Infectious causes of stroke. *Lancet Infect Dis*. 2014;14:869–880. doi: 10.1016/S1473-3099(14)70755-8
2. Bova IY, Bornstein NM, Korczyn AD. Acute infection as a risk factor for ischemic stroke. *Stroke*. 1996;27:2204–2206. doi: 10.1161/01.str.27.12.2204
3. Grau AJ, Buggle F, Heindl S, Steichen-Wiehn C, Banerjee T, Maiwald M, Rohlfs M, Suhr H, Fiehn W, Becher H. Recent infection as a risk factor for cerebrovascular ischemia. *Stroke*. 1995;26:373–379. doi: 10.1161/01.str.26.3.373
4. Grau AJ, Urbanek C, Palm F. Common infections and the risk of stroke. *Nat Rev Neurol*. 2010;6:681–694. doi: 10.1038/nrneurol.2010.163
5. Paganini-Hill A, Lozano E, Fischberg G, Perez Barreto M, Rajamani K, Ameriso SF, Heseltine PN, Fisher M. Infection and risk of ischemic stroke: differences among stroke subtypes. *Stroke*. 2003;34:452–457. doi: 10.1161/01.str.0000053451.28410.98
6. Nagel MA, Cohrs RJ, Mahalingam R, Wellish MC, Forghani B, Schiller A, Safdieh JE, Kamenkovich E, Ostrow LW, Levy M, et al. The varicella zoster virus vasculopathies: clinical, CSF, imaging, and virologic features. *Neurology*. 2008;70:853–860. doi: 10.1212/01.wnl.0000304747.38502.e8
7. Maginnis MS. Virus-receptor interactions: the key to cellular invasion. *J Mol Biol*. 2018;430:2590–2611. doi: 10.1016/j.jmb.2018.06.024
8. Lee HC, Chathuranga K, Lee JS. Intracellular sensing of viral genomes and viral evasion. *Exp Mol Med*. 2019;51:1–13. doi: 10.1038/s12276-019-0299-y
9. Takeuchi O, Akira S. Pattern recognition receptors and inflammation. *Cell*. 2010;140:805–820. doi: 10.1016/j.cell.2010.01.022
10. Ivashkiv LB, Donlin LT. Regulation of type I interferon responses. *Nat Rev Immunol*. 2014;14:36–49. doi: 10.1038/nri3581
11. Schneider WM, Chevillotte MD, Rice CM. Interferon-stimulated genes: a complex web of host defenses. *Annu Rev Immunol*. 2014;32:513–545. doi: 10.1146/annurev-immunol-032713-120231
12. Stegelmeier AA, van Vloten JP, Mould RC, Klafuric EM, Minott JA, Wootton SK, Bridle BW, Karimi K. Myeloid cells during viral infections and inflammation. *Viruses*. 2019;11:168. doi: 10.3390/v11020168
13. Samuel CE. Antiviral actions of interferons. *Clin Microbiol Rev*. 2001;14:778–809. doi: 10.1128/CMR.14.4.778-809.2001
14. Landman SL, Ressing ME, van der Veen AG. Balancing STING in antimicrobial defense and autoinflammation. *Cytokine Growth Factor Rev*. 2020;55:1–14. doi: 10.1016/j.cytogfr.2020.06.004
15. Newton AH, Cardani A, Braciale TJ. The host immune response in respiratory virus infection: balancing virus clearance and immunopathology. *Semin Immunopathol*. 2016;38:471–482. doi: 10.1007/s00281-016-0558-0
16. Ransohoff RM, Cardona AE. The myeloid cells of the central nervous system parenchyma. *Nature*. 2010;468:253–262. doi: 10.1038/nature09615
17. Klein RS, Garber C, Funk KE, Salimi H, Soung A, Kanmogne M, Manivasagam S, Agner S, Cain M. Neuroinflammation during RNA viral infections. *Annu Rev Immunol*. 2019;37:73–95. doi: 10.1146/annurev-immunol-042718-041417
18. Liddelow SA, Guttenplan KA, Clarke LE, Bennett FC, Bohlen CJ, Schirmer L, Bennett ML, Münch AE, Chung WS, Peterson TC, et al. Neurotoxic reactive astrocytes are induced by activated microglia. *Nature*. 2017;541:481–487. doi: 10.1038/nature21029
19. Lindqvist R, Mundt F, Gilthorpe JD, Wölfel S, Gekara NO, Kröger A, Överby AK. Fast type I interferon response protects astrocytes from flavivirus infection and virus-induced cytopathic effects. *J Neuroinflammation*. 2016;13:277. doi: 10.1186/s12974-016-0748-7
20. Zuza AL, Barros HL, de Mattos Silva Oliveira TF, Chávez-Pavoni JH, Zanon RG. Astrocyte response to St. Louis encephalitis virus. *Virus Res*. 2016;217:92–100. doi: 10.1016/j.virusres.2016.03.005
21. Cheng Y, King NJ, Kesson AM. Major histocompatibility complex class I (MHC-I) induction by West Nile virus: involvement of 2 signaling pathways in MHC-I up-regulation. *J Infect Dis*. 2004;189:658–668. doi: 10.1086/381501
22. Chevalier G, Suberbielle E, Monnet C, Duplan V, Martin-Blondel G, Farrugia F, Le Masson G, Liblau R, Gonzalez-Dunia D. Neurons are MHC class I-dependent targets for CD8 T cells upon neurotropic viral infection. *PLoS Pathog*. 2011;7:e1002393. doi: 10.1371/journal.ppat.1002393
23. Delhaye S, Paul S, Blakqori G, Minet M, Weber F, Staeheli P, Michiels T. Neurons produce type I interferon during viral encephalitis. *Proc Natl Acad Sci U S A*. 2006;103:7835–7840. doi: 10.1073/pnas.0602460103
24. van Timmeren MM, Heeringa P, Kallenberg CG. Infectious triggers for vasculitis. *Curr Opin Rheumatol*. 2014;26:416–423. doi: 10.1097/BOR.0000000000000068
25. Dal Canto AJ, Virgin HW. Animal models of infection-mediated vasculitis: implications for human disease. *Int J Cardiol*. 2000;75(suppl 1):S37–S45. doi: 10.1016/s0167-5273(00)00187-x
26. Mohan N, Kerr G. Infectious etiology of vasculitis: diagnosis and management. *Curr Rheumatol Rep*. 2003;5:136–141. doi: 10.1007/s11926-003-0041-5
27. Guillevin L, Mahr A, Callard P, Godmer P, Pagnoux C, Leray E, Cohen P; French Vasculitis Study Group. Hepatitis B virus-associated polyarteritis nodosa: clinical characteristics, outcome, and impact of treatment in 115 patients. *Medicine (Baltimore)*. 2005;84:313–322. doi: 10.1097/01.md.0000180792.80212.5e
28. Michalak T. Immune complexes of hepatitis B surface antigen in the pathogenesis of periarteritis nodosa. A study of seven necropsy cases. *Am J Pathol*. 1978;90:619–632.
29. Lavi E, Gilden D, Nagel M, White T, Grose C. Prevalence and distribution of VZV in temporal arteries of patients with giant cell arteritis. *Neurology*. 2015;85:1914–1915. doi: 10.1212/01.wnl.0000475335.63503.86
30. Gilden D, Nagel MA. Varicella zoster virus and giant cell arteritis. *Curr Opin Infect Dis*. 2016;29:275–279. doi: 10.1097/QCO.0000000000000258
31. Ridker PM. On evolutionary biology, inflammation, infection, and the causes of atherosclerosis. *Circulation*. 2002;105:2–4.
32. Numano F. Vasa vasoritis, vasculitis and atherosclerosis. *Int J Cardiol*. 2000;75(suppl 1):S1–S8. doi: 10.1016/s0167-5273(00)00196-0
33. Lee YH, Choi SJ, Ji JD, Song GG. Associations between the angiotensin-converting enzyme insertion/deletion polymorphism and susceptibility to vasculitis: a meta-analysis. *J Renin Angiotensin Aldosterone Syst*. 2012;13:196–201. doi: 10.1177/1470320311434240
34. Takahashi Y, Haga S, Ishizaka Y, Mimori A. Autoantibodies to angiotensin-converting enzyme 2 in patients with connective tissue diseases. *Arthritis Res Ther*. 2010;12:R85. doi: 10.1186/ar3012
35. Stoll G, Bendszus M. Inflammation and atherosclerosis: novel insights into plaque formation and destabilization. *Stroke*. 2006;37:1923–1932. doi: 10.1161/01.STR.0000226901.34927.10
36. Janoudi A, Shamoun FE, Kalavakunta JK, Abela GS. Cholesterol crystal induced arterial inflammation and destabilization of atherosclerotic plaque. *Eur Heart J*. 2016;37:1959–1967. doi: 10.1093/eurheartj/ehv653
37. Manduteanu I, Simionescu M. Inflammation in atherosclerosis: a cause or a result of vascular disorders? *J Cell Mol Med*. 2012;16:1978–1990. doi: 10.1111/j.1582-4934.2012.01552.x
38. Goeijenbier M, van Wissen M, van de Weg C, Jong E, Gerdes VE, Meijers JC, Brandjes DP, van Gorp EC. Review: Viral infections and mechanisms of thrombosis and bleeding. *J Med Virol*. 2012;84:1680–1696. doi: 10.1002/jmv.23354
39. Reffelmann T, Kloner RA. The "no-reflow" phenomenon: basic science and clinical correlates. *Heart*. 2002;87:162–168. doi: 10.1136/heart.87.2.162
40. Yau JW, Teoh H, Verma S. Endothelial cell control of thrombosis. *BMC Cardiovasc Disord*. 2015;15:130. doi: 10.1186/s12872-015-0124-z
41. Taylor FB Jr, Toh CH, Hoots WK, Wada H, Levi M; Scientific Subcommittee on Disseminated Intravascular Coagulation (DIC) of the International Society on Thrombosis and Haemostasis (ISTH). Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *Thromb Haemost*. 2001;86:1327–1330.
42. Nicholson AC, Hajjar DP. Herpesviruses and thrombosis: activation of coagulation on the endothelium. *Clin Chim Acta*. 1999;286:23–29. doi: 10.1016/s0009-8981(99)00091-1
43. Pryzdial EL, Sutherland MR, Ruf W. The procoagulant envelope virus surface: contribution to enhanced infection. *Thromb Res*. 2014;133(suppl 1):S15–S17. doi: 10.1016/j.thromres.2014.03.010
44. Sutherland MR, Friedman HM, Pryzdial EL. Thrombin enhances herpes simplex virus infection of cells involving protease-activated receptor 1. *J Thromb Haemost*. 2007;5:1055–1061. doi: 10.1111/j.1538-7836.2007.02441.x

45. Sutherland MR, Ruf W, Pryzdial EL. Tissue factor and glycoprotein C on herpes simplex virus type 1 are protease-activated receptor 2 cofactors that enhance infection. *Blood*. 2012;119:3638–3645. doi: 10.1182/blood-2011-08-376814
46. Teijaro JR, Walsh KB, Cahalan S, Fremgen DM, Roberts E, Scott F, Martinborough E, Peach R, Oldstone MB, Rosen H. Endothelial cells are central orchestrators of cytokine amplification during influenza virus infection. *Cell*. 2011;146:980–991. doi: 10.1016/j.cell.2011.08.015
47. Beristain-Covarrubias N, Perez-Toledo M, Thomas MR, Henderson IR, Watson SP, Cunningham AF. Understanding infection-induced thrombosis: lessons learned from animal models. *Front Immunol*. 2019;10:2569. doi: 10.3389/fimmu.2019.02569
48. Schultz JC, Hilliard AA, Cooper LT Jr, Rihal CS. Diagnosis and treatment of viral myocarditis. *Mayo Clin Proc*. 2009;84:1001–1009. doi: 10.1016/S0025-6196(11)60670-8
49. Maino A, Rosendaal FR, Algra A, Peyvandi F, Siegerink B. Hypercoagulability is a stronger risk factor for ischaemic stroke than for myocardial infarction: a systematic review. *PLoS One*. 2015;10:e0133523. doi: 10.1371/journal.pone.0133523
50. Ichiki H, Orihara K, Hamasaki S, Ishida S, Oketani N, Iriki Y, Ninomiya Y, Okui H, Kuwahata S, Fujita S, et al. The role of infection in the development of non-valvular atrial fibrillation: up-regulation of Toll-like receptor 2 expression levels on monocytes. *J Cardiol*. 2009;53:127–135. doi: 10.1016/j.jjcc.2008.09.008
51. Paget C, Trottein F. Mechanisms of bacterial superinfection post-influenza: a role for unconventional T cells. *Front Immunol*. 2019;10:336. doi: 10.3389/fimmu.2019.00336
52. Ding R, Wang Z, Lin Y, Liu B, Zhang Z, Ma X. Comparison of a new criteria for sepsis-induced coagulopathy and International Society on Thrombosis and Haemostasis disseminated intravascular coagulation score in critically ill patients with sepsis 3.0: a retrospective study. *Blood Coagul Fibrinolysis*. 2018;29:551–558. doi: 10.1097/MBC.0000000000000755
53. Lin GL, McGinley JP, Drysdale SB, Pollard AJ. Epidemiology and immune pathogenesis of viral sepsis. *Front Immunol*. 2018;9:2147. doi: 10.3389/fimmu.2018.02147
54. Lip GY, Blann AD, Farooqi IS, Zarifis J, Sagar G, Beevers DG. Sequential alterations in haemorheology, endothelial dysfunction, platelet activation and thrombogenesis in relation to prognosis following acute stroke: The West Birmingham Stroke Project. *Blood Coagul Fibrinolysis*. 2002;13:339–347. doi: 10.1097/00001721-200206000-00010
55. Trangmar SJ, Chiesa ST, Llodio I, Garcia B, Kalsi KK, Secher NH, González-Alonso J. Dehydration accelerates reductions in cerebral blood flow during prolonged exercise in the heat without compromising brain metabolism. *Am J Physiol Heart Circ Physiol*. 2015;309:H1598–H1607. doi: 10.1152/ajpheart.00525.2015
56. Tsai YH, Yang JL, Lee IN, Yang JT, Lin LC, Huang YC, Yeh MY, Weng HH, Su CH. Effects of dehydration on brain perfusion and infarct core after acute middle cerebral artery occlusion in rats: evidence from high-field magnetic resonance imaging. *Front Neurol*. 2018;9:786. doi: 10.3389/fneur.2018.00786
57. Bahouth MN, Gottesman RF, Szanton SL. Primary 'dehydration' and acute stroke: a systematic research review. *J Neurol*. 2018;265:2167–2181. doi: 10.1007/s00415-018-8799-6
58. Ducros A. Reversible cerebral vasoconstriction syndrome. *Lancet Neurol*. 2012;11:906–917. doi: 10.1016/S1474-4422(12)70135-7
59. Saylor D, Thakur K, Venkatesan A. Acute encephalitis in the immunocompromised individual. *Curr Opin Infect Dis*. 2015;28:330–336. doi: 10.1097/QCO.0000000000000175
60. John AR, Canaday DH. Herpes zoster in the older adult. *Infect Dis Clin North Am*. 2017;31:811–826. doi: 10.1016/j.idc.2017.07.016
61. George BP, Schneider EB, Venkatesan A. Encephalitis hospitalization rates and inpatient mortality in the United States, 2000-2010. *PLoS One*. 2014;9:e104169. doi: 10.1371/journal.pone.0104169
62. Mailles A, Stahl JP; Steering Committee and Investigators Group. Infectious encephalitis in france in 2007: a national prospective study. *Clin Infect Dis*. 2009;49:1838–1847. doi: 10.1086/648419
63. Glaser CA, Honarmand S, Anderson LJ, Schnurr DP, Forghani B, Cossen CK, Schuster FL, Christie LJ, Tureen JH. Beyond viruses: clinical profiles and etiologies associated with encephalitis. *Clin Infect Dis*. 2006;43:1565–1577. doi: 10.1086/509330
64. Gilden D, Nagel MA, Cohrs RJ, Mahalingam R. The variegate neurological manifestations of varicella zoster virus infection. *Curr Neurol Neurosci Rep*. 2013;13:374. doi: 10.1007/s11910-013-0374-z
65. Sadaoka T, Depledge DP, Rajbhandari L, Venkatesan A, Breuer J, Cohen JI. In vitro system using human neurons demonstrates that varicella-zoster vaccine virus is impaired for reactivation, but not latency. *Proc Natl Acad Sci U S A*. 2016;113:E2403–E2412. doi: 10.1073/pnas.1522575113
66. Askalan R, Laughlin S, Mayank S, Chan A, MacGregor D, Andrew M, Curtis R, Meaney B, deVeber G. Chickenpox and stroke in childhood: a study of frequency and causation. *Stroke*. 2001;32:1257–1262. doi: 10.1161/01.str.32.6.1257
67. Ganesan V, Kirkham FJ. Mechanisms of ischaemic stroke after chickenpox. *Arch Dis Child*. 1997;76:522–525. doi: 10.1136/adc.76.6.522
68. Eidelberg D, Sotrel A, Horoupian DS, Neumann PE, Pumarola-Sune T, Price RW. Thrombotic cerebral vasculopathy associated with herpes zoster. *Ann Neurol*. 1986;19:7–14. doi: 10.1002/ana.410190103
69. Gilden D, Cohrs RJ, Mahalingam R, Nagel MA. Varicella zoster virus vasculopathies: diverse clinical manifestations, laboratory features, pathogenesis, and treatment. *Lancet Neurol*. 2009;8:731–740. doi: 10.1016/S1474-4422(09)70134-6
70. Gilden DH, Kleinschmidt-DeMasters BK, LaGuardia JJ, Mahalingam R, Cohrs RJ. Neurologic complications of the reactivation of varicella-zoster virus. *N Engl J Med*. 2000;342:635–645. doi: 10.1056/NEJM200003023420906
71. Steain M, Slobedman B, Abendroth A. Experimental models to study varicella-zoster virus infection of neurons. *Curr Top Microbiol Immunol*. 2010;342:211–228. doi: 10.1007/82_2010_15
72. Cohen JI. Rodent models of varicella-zoster virus neurotropism. *Curr Top Microbiol Immunol*. 2010;342:277–289. doi: 10.1007/82_2010_11
73. Nagel MA, Traktinskiy I, Azarkh Y, Kleinschmidt-DeMasters B, Hedley-Whyte T, Russman A, VanEgmond EM, Stenmark K, Frid M, Mahalingam R, et al. Varicella zoster virus vasculopathy: analysis of virus-infected arteries. *Neurology*. 2011;77:364–370. doi: 10.1212/WNL.0b013e3182267bfa
74. Nagel MA, Traktinskiy I, Stenmark KR, Frid MG, Choe A, Gilden D. Varicella-zoster virus vasculopathy: immune characteristics of virus-infected arteries. *Neurology*. 2013;80:62–68. doi: 10.1212/WNL.0b013e31827b1ab9
75. Jones D, Alvarez E, Selva S, Gilden D, Nagel MA. Proinflammatory cytokines and matrix metalloproteinases in CSF of patients with VZV vasculopathy. *Neurol Neuroimmunol Neuroinflamm*. 2016;3:e246. doi: 10.1212/NXI.0000000000000246
76. Nagel MA, Jones D, Wyborny A. Varicella zoster virus vasculopathy: the expanding clinical spectrum and pathogenesis. *J Neuroimmunol*. 2017;308:112–117. doi: 10.1016/j.jneuroim.2017.03.014
77. Eleftheriou D, Moraitis E, Hong Y, Turmaine M, Venturini C, Ganesan V, Breuer J, Klein N, Brogan P. Microparticle-mediated VZV propagation and endothelial activation: mechanism of VZV vasculopathy. *Neurology*. 2020;94:e474–e480. doi: 10.1212/WNL.0000000000008885
78. Ostrowski RA, Metgud S, Tehrani R, Jay WM. Varicella zoster virus in giant cell arteritis: a review of current medical literature. *Neuroophthalmology*. 2019;43:159–170. doi: 10.1080/01658107.2019.1604763
79. Elkind MS, Carty CL, O'Meara ES, Lumley T, Lefkowitz D, Kronmal RA, Longstreth WT Jr. Hospitalization for infection and risk of acute ischemic stroke: the Cardiovascular Health Study. *Stroke*. 2011;42:1851–1856. doi: 10.1161/STROKEAHA.110.608588
80. Miller EC, Elkind MS. Infection and stroke: an update on recent progress. *Curr Neurol Neurosci Rep*. 2016;16:2. doi: 10.1007/s11910-015-0602-9
81. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. *N Engl J Med*. 2004;351:2611–2618. doi: 10.1056/NEJMoa041747
82. Boehme AK, Luna J, Kulick ER, Kamel H, Elkind MSV. Influenza-like illness as a trigger for ischemic stroke. *Ann Clin Transl Neurol*. 2018;5:456–463. doi: 10.1002/acn3.545
83. Muhammad S, Haasbach E, Kotchourko M, Strigli A, Krenz A, Ridder DA, Vogel AB, Marti HH, Al-Abed Y, Planz O, et al. Influenza virus infection aggravates stroke outcome. *Stroke*. 2011;42:783–791. doi: 10.1161/STROKEAHA.110.596783
84. Merkler AE, Parikh NS, Mir S, Gupta A, Kamel H, Lin E, Lantos J, Schenck EJ, Goyal P, Bruce SS, et al. Risk of ischemic stroke in patients with coronavirus disease 2019 (COVID-19) vs patients with influenza. *JAMA Neurol*. 2020; 77:1366–1372. doi: 10.1001/jamaneurol.2020.2730
85. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, De Leacy RA, Shigematsu T, Ladner TR, Yaeger KA, et al. Large-vessel stroke as a presenting feature of Covid-19 in the young. *N Engl J Med*. 2020;382:e60. doi: 10.1056/NEJMc2009787
86. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, et al. Neurologic manifestations of hospitalized patients with coronavirus

disease 2019 in Wuhan, China. *JAMA Neurol*. 2020;77:683–690. doi: 10.1001/jamaneurol.2020.1127
87. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395:1054–1062. doi: 10.1016/S0140-6736(20)30566-3
88. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, Collange O, Boulay C, Fafi-Kremer S, Ohana M, et al. Neurologic features in severe SARS-CoV-2 infection. *N Engl J Med*. 2020;382:2268–2270. doi: 10.1056/NEJMc2008597
89. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. *Blood*. 2020;135:2033–2040. doi: 10.1182/blood.2020006000
90. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: a review. *JAMA Cardiol*. 2020;5:831–840. doi: 10.1001/jamacardio.2020.1286
91. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol*. 2004;203:631–637. doi: 10.1002/path.1570
92. To KF, Lo AW. Exploring the pathogenesis of severe acute respiratory syndrome (SARS): the tissue distribution of the coronavirus (SARS-CoV) and its putative receptor, angiotensin-converting enzyme 2 (ACE2). *J Pathol*. 2004;203:740–743. doi: 10.1002/path.1597
93. Divani AA, Andalib S, Di Napoli M, Lattanzi S, Hussain MS, Biller J, McCullough LD, Azarpazhooh MR, Seletska A, Mayer SA, et al. Coronavirus disease 2019 and stroke: clinical manifestations and pathophysiological insights. *J Stroke Cerebrovasc Dis*. 2020;29:104941. doi: 10.1016/j.jstrokecerebrovasdis.2020.104941
94. Labò N, Ohnuki H, Tosato G. Vasculopathy and coagulopathy associated with SARS-CoV-2 infection. *Cells*. 2020; 9:1583. doi: 10.3390/cells9071583
95. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497–506. doi: 10.1016/S0140-6736(20)30183-5
96. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med*. 2020;46:846–848. doi: 10.1007/s00134-020-05991-x
97. Bhaskar S, Sinha A, Banach M, Mittoo S, Weissert R, Kass JS, Rajagopal S, Pai AR, Kutty S. Cytokine storm in COVID-19-immunopathological mechanisms, clinical considerations, and therapeutic approaches: the REPROGRAM consortium position paper. *Front Immunol*. 2020;11:1648. doi: 10.3389/fimmu.2020.01648
98. Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. *Cold Spring Harb Perspect Biol*. 2014;6:a016295. doi: 10.1101/cshperspect.a016295
99. Bastard P, Rosen LB, Zhang Q, Michailidis E, Hoffmann HH, Zhang Y, Dorgham K, Philippot Q, Rosain J, Béziat V, et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. *Science*. 2020;370:eabd4585. doi: 10.1126/science.abd4585
100. Hadjadj J, Yatim N, Barnabei L, Corneau A, Boussier J, Smith N, Péré H, Charbit B, Bondet V, Chenevier-Gobeaux C, et al. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. *Science*. 2020;369:718–724. doi: 10.1126/science.abc6027
101. Zhang Q, Bastard P, Liu Z, Le Pen J, Moncada-Velez M, Chen J, Ogishi M, Sabli IKD, Hodeib S, Korol C, et al. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. *Science*. 2020;370:eabd4570. doi: 10.1126/science.abd4570
102. Akbar AN, Gilroy DW. Aging immunity may exacerbate COVID-19. *Science*. 2020;369:256–257. doi: 10.1126/science.abb0762
103. Favalli EG, Ingegnoli F, De Lucia O, Cincinelli G, Cimaz R, Caporali R. COVID-19 infection and rheumatoid arthritis: Faraway, so close! *Autoimmun Rev*. 2020;19:102523. doi: 10.1016/j.autrev.2020.102523
104. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, Vanstapel A, Werlein C, Stark H, Tzankov A, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med*. 2020;383:120–128. doi: 10.1056/NEJMoa2015432
105. Lowenstein CJ, Solomon SD. Severe COVID-19 is a microvascular disease. *Circulation*. 2020;142:1609–1611. doi: 10.1161/CIRCULATIONAHA.120.050354
106. Perlman S, Evans G, Afifi A. Effect of olfactory bulb ablation on spread of a neurotropic coronavirus into the mouse brain. *J Exp Med*. 1990;172:1127–1132. doi: 10.1084/jem.172.4.1127
107. Desforges M, Le Coupanec A, Stodola JK, Meessen-Pinard M, Talbot PJ. Human coronaviruses: viral and cellular factors involved in neuroinvasiveness and neuropathogenesis. *Virus Res*. 2014;194:145–158. doi: 10.1016/j.virusres.2014.09.011