Editorial

Tissue Plasminogen Activator for Stroke and Concomitant Influenza Infection
Is This a Dangerous Combination?

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See related article, pages 783–791.

In individuals with a vascular risk profile, the occurrence of stroke is not equally distributed over time. In fact, there are trigger factors that temporarily increase the risk of stroke. Acute and exacerbating chronic infections are among such trigger factors. Mainly respiratory tract infections and both bacterial and viral infection appear to be important in this respect. Influenza virus infection is among the infections that play a relevant role, probably not only by direct viral infection, but also through bacterial superinfections. Large epidemiological surveys had shown that the mortality from cardiovascular disease and stroke increases in temporal association with influenza epidemics and that vascular disease contributes to a large degree to influenza-related mortality. Furthermore, case–control and large observational studies reported that influenza vaccination is associated with reduced hospitalization for and mortality of stroke and myocardial infarction. Although causality is not firmly proven, it is very likely that influenza vaccination exerts protective effects regarding vascular diseases and therefore recent guidelines on secondary prevention for cardiovascular diseases have included influenza infection.

Infection, thrombosis, and ischemic stroke are potentially linked with each other by a multitude of connective pathways; however, the induction of a procoagulant state through inflammatory mechanisms probably plays a central role. One of the multiple pathways involves the antigen-specific expansion of effector T cells in unstable carotid plaques with influenza A virus among the driving antigens, a mechanism that could explain the occurrence of large artery atherothrombotic stroke during influenza infection.

However, the effect of concomitant influenza infection on the pathophysiology of ischemic stroke has not been well studied so far. Here comes the article by Muhammed and coworkers that adds numerous new insights to our previous knowledge. It is an important piece of work that uses influenza virus inoculation 2 to 5 days before permanent middle cerebral artery occlusion in a mouse model and includes a large bunch of valuable and thoughtful experiments. The study shows that influenza infection 3 to 5 days before permanent middle cerebral artery occlusion increases infarct size but not mortality, a finding probably not explained by mild hypoxemia after influenza infection according to the experiments. Direct brain infection by influenza viruses did most likely not play a role in stroke aggravation. In lung tissue, the concentration of several cytokines, including RANTES, were increased in influenza infection reflected by an enhanced expression of cytokines such as interleukin-1β, monocyte chemoattractant protein-1, macrophage inflammatory protein-2, tumor necrosis factor, and others in the brain in concomitant stroke but not in stroke-free animals. In plasma, RANTES levels were increased and this substance and potentially other cytokines may induce the increased expression of inflammatory mediators in ischemic brain. Several of the cytokines expressed in the ischemic brain contribute to neutrophil recruitment and, in fact, a higher number of neutrophils was detected in influenza-infected mice paralleled by increased levels of matrix metalloproteinase-9, a neutrophil-derived enzyme degrading extracellular matrix proteins and by aggravated disruption of the blood–brain barrier. Importantly, tissue plasminogen activator use in humans with concomitant infection could be more riskful than in noninfected subjects. In fact, increased matrix metalloproteinase-9 concentration after tissue plasminogen activator treatment was associated with increased volume of intracerebral hemorrhage, an effect possibly caused by increased matrix metalloproteinase-9 activity. This could mean, as outlined by the authors, that tissue plasminogen activator use in humans with concomitant infection could be more riskful than in noninfected subjects. In fact, increased matrix metalloproteinase-9 concentration after tissue plasminogen activator treatment was shown to be related to hemorrhagic transformation after ischemic stroke. This topic of a possible increased risk of tissue plasminogen activator in patients with concomitant infection certainly requires further exploration in clinical studies.

The study by Muhammed et al goes 1 step further and shows that lowering of RANTES plasma concentration by GTS, a selective agonist of the α7 nicotinic acetylcholine receptor, reduced infarct size in influenza-infected mice but not in noninfected animals and improved survival. Thus, the study also gives an innovative hint about how infarct enlargement associated with influenza infection may be counteracted in the future. Actually, infarct size in influenza-infected mice was increased in permanent but not in temporary middle cerebral artery occlusion in this study. The reason for such difference is not obvious. Case–control studies in human stroke also do not give a clear picture regarding stroke severity in infection-associated stroke with some but not all studies showing...
greater stroke severity after infection. The interplay between infection and organ ischemia is most complicated. Proinflammatory cytokine-induced cascades play a major role in stroke aggravation as shown in this intriguing study. On the other hand, pretreatment with lipopolysaccharide, as a paradigm of Gram-negative infection, can also reduce tissue injury when given in subinjurious dosages, a phenomenon termed lipopolysaccharide preconditioning analogous to ischemic preconditioning. The timing and severity of infection may thus have differential effects on stroke severity, although further studies (eg, with viral infections) are required in this field.

Muhammed and coworkers infected young and previously healthy animals and induced stroke artificially in their mice. Approximately 2 decades ago, John Hallenbeck’s group showed that lipopolysaccharide application induced infarctions in the brain stem in aged, in hypertensive, and in stroke-prone rats but not in young and healthy animals. It would be highly interesting to know whether influenza infection would induce (subclinical) cerebral ischemia in aged and risk factor-positive rodents. This would not be completely astonishing given the findings that patients who have died after infections, including influenza, can show severe arterial lesions.

The study by Muhammed and coworkers tells us an exciting story built up in several chapters and—like every innovative scientific article—it opens 1 door and now we find ourselves in a floor with many still closed doorways the keys to which we still have to find.

Disclosures
The author received honoraria for serving on a Data and Safety Monitoring Board of a large influenza vaccine study in 2010.

References
5. Davis MM, Taubert K, Benin AL, Brown DW, Mensah GA, Baddour LM, Dunbar S, Krumholz HM; American Heart Association; American College of Cardiology; American Association of Cardiovascular and Pulmonary Rehabilitation; American Association of Critical Care Nurses; American Association of Heart Failure Nurses; American Diabetes Association; Association of Black Cardiologists, Inc; Heart Failure Society of America; Preventive Cardiovascular Nurses Association; American Academy of Nurse Practitioners; Centers for Disease Control and Prevention and the Advisory Committee on Immunization. Influenza vaccination as secondary prevention for cardiovascular disease: a science advisory from the American Heart Association/American College of Cardiology. *J Am Coll Cardiol*. 2006;48:1498–1502.

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