Infection as cause of stroke

A contagious idea that may explain racial disparity

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In the aftermath of an acute cardiovascular event such as stroke, patients and families frequently ask whether preceding circumstances such as viral illnesses, stress, and other medical or surgical events brought on the disease. Although it seems intuitive to patients and families that acute precipitants or disease triggers play a substantial role, the evidence to support this concept has accumulated slowly.[1,2] Support for acute systemic infection as a trigger of stroke, a particularly interesting hypothesis, continues to grow.[3] The potential mechanisms underlying such a relationship include systemic inflammation, endothelial dysfunction, and activation of the clotting system by infectious organisms or the systemic response to them.[4,5]

Although on the face of it seemingly unrelated, the contribution of race and ethnicity to stroke risk has garnered substantial attention. After sifting through the nuances of race and ethnicity, one can determine that there is an increased risk of stroke mortality for certain ethnic groups, including non-Hispanic blacks.[6,7] Although stroke mortality for all races has declined in the last few decades, non-Hispanic black populations have seen more modest declines than non-Hispanic white populations.[7] The most common explanations for this excess risk include discrepancies in risk factor profile, stroke incidence, and socioeconomic status; however, a portion of the discrepancy remains unexplained.[7]

In this issue of *Neurology*®, Levine et al.[8] stitch together these disparate risk factors. These investigators examined a nationally representative cohort of older Americans to test the relationship between preceding infection and risk for stroke and stroke mortality in 3 race/ethnic groups: non-Hispanic white, non-Hispanic black, and Hispanic. Their effort accomplishes 2 goals. It provides additional support for infection as a risk factor for stroke. It also attempts, in a novel way, to explain racial discrepancies in stroke mortality on the basis of an increased burden of infection. The case crossover methodology, which uses the patients themselves at different time points as their own controls, enabled the investigators to analyze the interaction between ethnicity and infection while reducing confounding by such factors as socioeconomic status.

The study found that for non-Hispanic whites and blacks, stroke occurrence was associated with an increased chance of exposure to infection in the preceding 2 weeks or 30 days. Even more striking was the strength of the relationship between stroke mortality and preceding infection for all 3 ethnic groups. Infection had a much larger effect on increased mortality for blacks compared to whites. There was nearly as impressive a relationship between stroke mortality and infection for those <70 years of age and obese patients (with limitations discussed below).

The authors acknowledge previous work suggesting an association between acute infection and atrial fibrillation that could explain some of the observed increased risk for stroke or stroke mortality in their study.[9] However, even after adjusting for atrial fibrillation, infection remained strongly associated with stroke occurrence and mortality in all racial groups and particularly in non-Hispanic blacks.

The results pose a number of questions that need to be answered. Patients had infections at other times, but infection during the preceding 14–30 days was more strongly linked to stroke. Stroke mortality had a particularly strong relationship with infections that occurred in the inpatient setting and this was particularly the case for blacks. This finding could reflect poorer inpatient stroke care in non-Hispanic blacks or alternatively could reflect greater disease severity, but the study could not address those additional factors. In addition, other noninfectious medical comorbidities not measured in the study could have occurred at greater frequency in blacks to account for some of the discrepancy in stroke mortality.

The article has other limitations. Importantly, despite the strength of the associations observed, the relatively small numbers of patients who were black or <70 years old or obese, with only 15 to 44 patients, resulted in very broad confidence intervals for the odds ratios.

Due to these limitations, the results should be corroborated in another study before we conclude

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definitively that infection is an intermediary in the relationship between race and stroke mortality. Still, this study (1) provides important confirmatory data of a link between stroke and preceding infection; (2) demonstrates a consistent relationship between preceding infection and stroke mortality across all ethnic groups studied; and (3) provides novel but preliminary data that preceding infection might contribute to the excess stroke mortality observed in non-Hispanic blacks.

Future research must determine whether discrepancies in quality of care poststroke explain the increase in exposure to infection for non-Hispanic blacks and whether this represents a target for intervention to reduce the discrepant mortality rates. In the meantime, stroke clinicians must strive to reduce infectious complications in all inpatients with stroke, which includes early removal of indwelling catheters to avoid urinary tract infections and careful screening for swallowing dysfunction to avoid aspiration pneumonia. Finally, considering that at least one randomized trial in the literature suggests a reduction in recurrent cardiovascular events with immunization for influenza, "get your flu shot" remains good advice for clinicians and patients alike.[10]

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