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Age-Related Macular Degeneration

Why Should Stroke Physicians Care?

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Age-related macular degeneration (AMD) is a chronic degenerative disease of the macula (central part of the retina) that in its late or advanced stage results in progressive loss of central vision.¹ There are 2 stages of this disease: early AMD, characterized by the appearance of a lipid-like deposit called drusen, and late AMD, in which patients have loss of vision as a consequence of 1 of 2 processes: geographic atrophy or neovascularization. In geographic atrophy (“dry” AMD), there is confluent atrophy of the choriocapillaries and associated retinal pigment epithelium. In neovascular (“wet”) AMD, there is an ingrowth of new vessels in the choroid that invades the retina, resulting in leakage of serous fluid, lipids, and blood with subsequent fibrous scarring.

Although most stroke physicians are aware that AMD is an important cause of vision loss in elderly persons,² many may not be aware that AMD and stroke are actually very similar diseases. Both conditions share common vascular risk factors (eg, smoking, hypertension), pathogenic mechanisms (eg, carotid artery disease, inflammation), and possibly even genetic factors (APOE genes).³

However, why should AMD interest stroke physicians? Two recent developments are relevant. First, there is emerging evidence that patients with AMD are at increased risk of developing a stroke over and above the expected risk seen in patients of similar age and vascular risk factors.⁴⁻⁷ In the Atherosclerosis Risk In Communities (ARIC) Study, persons with early AMD signs had double the risk of incident stroke over 10 years.⁵ This association was present while controlling for common risk factors between AMD and stroke. Similar findings have been reported from a survey of 1.4 million Medicare enrollees, which found 20% to

30% higher 2-year risk of stroke among patients with neovascular AMD as compared with control subjects.⁶

In the current issue of *Stroke*, Hu and colleagues further report on this association.⁸ Using a national linkage database in Taiwan, the authors showed that patients with a neovascular AMD diagnosis had a 2-fold higher incidence of stroke than those without AMD (18.2% versus 9.9%), and this association persisted while controlling for concomitant vascular risk factors. One of the strengths of this study is the ability to study neovascular AMD cases; in population-based studies like the ARIC cohort, there were few late neovascular AMDs. Limitations of the study include the lack of clinical validation to confirm the diagnosis of neovascular AMD, lack of comparative data to determine the association with geographic atrophy or early AMD, and the fact that Chinese persons are more likely to have polypoidal choroidal vasculopathy, a particular variant of neovascular AMD that may have a more “vascular etiology,”⁹ which may limit the generalizability of these results to other populations, particularly whites. Nevertheless, these data provide additional compelling evidence that AMD is associated with underlying systemic vascular disease and is a risk marker for stroke.

Second, stroke physicians should be aware of new treatments for neovascular AMD. The introduction of therapies blocking vascular endothelial growth factor (VEGF), a major pathogenic factor for neovascular AMD, represents a landmark in the management of this disease.¹⁰ It is now routine for patients with neovascular AMD to have regular monthly to 2 monthly intraocular injections of anti-VEGF agents (eg, ranibizumab, bevacizumab). However, a persistent concern regarding anti-VEGF treatment is the potential increased risk of stroke.⁴ This is based on knowledge that VEGF is essential for new vessel growth, including the formation of collaterals in the brain, the myocardium, and in other tissues. In theory, intraocular injections of anti-VEGF agents for treatment of AMD are safe, because they are given in small doses and into the vitreous cavity. In the 2 pivotal trials to date, monthly intravitreal injections of ranibizumab over 2 years were not associated with an increased risk of stroke or other vascular events as compared with placebo.^{11,12} However, in an analysis of these 2 trials, there was a statistically significant increased rate of nonocular hemorrhage, including cerebral hemorrhage, in patients treated with ranibizumab.¹³ An interim analysis of another trial reported an increased risk of stroke with the higher as compared with lower doses of

ranibizumab (1.2% versus 0.3%, $P=0.02$), although final data analyses at study completion showed no significant increased risk of stroke.¹⁴ In meta-analysis of current trials, there appears to be a trend toward a higher risk of stroke among persons with a history of stroke or arrhythmias treated with higher ranibizumab doses.¹⁵ It should be emphasized, however, that the current clinical trials are not statistically powered to detect small risk differences in stroke risk, and because anti-VEGF treatment for neovascular AMD is likely needed for many years, adverse effects due to long-term VEGF suppression on the cerebral vasculature will not be immediately apparent.

Thus, physicians should be alerted to the possibility of an increased risk of stroke in elderly patients with AMD and that this risk may be further accentuated by the use of anti-VEGF therapy.